Bioinspired stereoselective synthesis of chiral 2,5-diaryl-3,4-dimethyltetrahydrofurans from unprotected 1,4-diarylbutane-1,4-diols

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Abstract

A bioinspired stereoselective synthesis of (2,3-anti-3,4-syn-4,5-anti)-2,5-diaryl-3,4-dimethyltetrahydrofurans from unprotected chiral 1,4-diarylbutane-1,4-diols is described. Upon treatment of the chiral 1,4-diarylbutane-1,4-diols with acid, chiral 2,5-diaryl-3,4-dimethyltetrahydrofurans were obtained in high yields and high stereoselectivity through the chemoselective formation of a more stabilized benzylic carbocation followed by a stereoselective cyclization. Proposely, the carbocation formation was chemoselectively governed by the substitution patterns of the non-symmetrical aryl groups of the 1,4-diarylbutane-1,4-diols and the stereoselective cyclization of the carbocation was inherently controlled by the stereochemistry of the substrates. The present study highlights a practical and an atom-economic process and provides essential information applicable for further design of the asymmetric synthesis of naturally occurring 2,5-diaryl-3,4-dimethyltetrahydrofurans and their derivatives isolated from *Krameria cystisoides*.

Keywords: Natural products, lignans, 2,5-diaryl-3,4-dimethyltetrahydrofurans, asymmetric synthesis

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The development of synthetic methodologies to access enantioenriched 2,5-diaryl-3,4-dimethyltetrahydrofurans which are important members of classical lignans remains highly important in the organic synthesis community. Among the developed methods, the syntheses based on bioinspired processes received considerable attention. 

Biosynthetically, 2,5-diaryl-3,4-dimethyltetrahydrofurans are proposed to be derived from the oxidative dimerization of two C6–C3 units, such as coniferyl alcohol or isoeugenol, with a β-β’ linkage pattern to form a quinone methide intermediate A followed by hydration (Scheme 1). Alternatively, biosynthetic pathway via dimerization of C6–C3 units, such as sinapyl alcohol, followed by oxidation and dehydration of 1,4-diarylbutane diols B was also proposed. Based on the latter biosynthetic pathway, a number of reports on the synthesis of 2,5-diaryl-3,4-dimethyltetrahydrofurans, both racemic and chiral forms, employing B as key advanced intermediates have been complied.

In general, a racemic synthesis of 2,5-diaryl-3,4-dimethyltetrahydrofurans from 1,4-diarylbutane-1,4-diols B bearing two symmetrical aromatic (Ar) groups could be readily achieved via Lewis acid-mediated cyclization (Scheme 2a). On the contrary, to access chiral 2,5-diaryl-3,4-dimethyltetrahydrofurans, asymmetric transformation of chiral 1,4-diarylbutane-1,4-diols B, especially those containing non-symmetrical Ar rings, is highly challenging from both chemo- and stereoselectivity points of view. Thus, the synthesis of chiral 2,5-diaryl-3,4-dimethyltetrahydrofurans bearing two different aryl groups usually required selective protection and activation of the two unidentical hydroxy groups (Scheme 2b). With an atom-economy concern, a synthetic strategy that allows simple and direct transformation of chiral 1,4-diarylbutane-1,4-diols B to chiral 2,5-diaryl-3,4-dimethyltetrahydrofurans in a chemo- and stereoselective manner is highly desirable and deserves investigation.

Having been interested on the synthetic approach to access chiral 2,5-diaryl-3,4-dimethyltetrahydrofurans bearing 2,3-anti-3,4-syn-4,5-anti relative stereochemistry, we primarily investigated an acid-catalyzed reaction of chiral 1,4-diarylbutane-1,4-diols 1 and 2. The results from this work would provide an insight on the factors that govern chemoselective formation of carbocations followed by their stereoselective cyclization reactions to chiral 1,4-diarylbutane-1,4-diols 1 and 2 (Scheme 2c). Therefore, the chiral 1,4-diarylbutane-1,4-diols 1 and 2 bearing two different aryl groups (Ar¹ and Ar²) where each has a different number of electron donating groups (EDGs) were designed and synthesized. On the basis that electron-rich Ar assisting carbocation formation, acid-catalyzed reaction of 1 should preferably lead to a carbocation intermediate C.
while 2 should give D. Additionally, two diastereoisomers for each of 1 and 2 were also designed and prepared for a detailed study on both chemo- and stereoselectivity of these reactions. In the cyclization step, the stereoselectivity of cyclization should be controlled by the steric effect resulting from the inherent stereochemistry of the two adjacent methyl groups. Thus, C would readily undergo cyclization leading to 3 as a single product while D should give a mixture of 3 and 4, respectively. The application of the present study to synthesize a natural product derivative and the confirmation of the absolute configurations of 2,5-diaryl-3,4-dimethyltetrahydrofurans isolated from Krameria cystisoides were demonstrated.\textsuperscript{18,19}

### Results and Discussion

The chiral 1,4-diarylbutane-1,4-diol 1 (Ar\textsuperscript{1}/Ar\textsuperscript{2} = mono-/di-EDGs) was first prepared (Scheme 3). The reaction of Weinreb amide (2R,3R)-5 (dr = 92:8)\textsuperscript{16} with 4-methoxyphenyllithium, freshly prepared from Li/Br exchange reaction between 4-bromo-1-methoxybenzene and n-BuLi, gave the corresponding (2R,3R)-ketone 6 in 69% yield (dr = 92:8). Ketone (2R,3R)-6 was then treated with NaBH\textsubscript{4} in MeOH at −78 to 0 °C to provide the (1R,2R,3R)-alcohol 7 (85% yield) as an inseparable diastereomeric mixture (dr = 81:11:8, \textsuperscript{1}H NMR analysis). Similar results were observed when DIBAL-H was employed as a reducing agent in THF at −78 °C. The stereochemical outcome of the hydride reduction to give (1R,2R,3R)-7 as a major diastereomer could be explained on the basis of the Felkin–Anh model; the coupling constants (\textsuperscript{3}J\textsubscript{H1,2}) of (1R,2R,3R)-7 and two diastereomers are 9.3, 6.4, and 9.0 Hz, respectively (see the Supplementary Material). Protection of a hydroxy group of (1R,2R,3R)-7 gave the TBS-ether (1R,2R,3R)-8 in 94% yield; with a dr = 83:11:6. Next, an oxidative cleavage of the alkene moiety of (1R,2R,3R)-8 followed by treatment of the obtained aldehyde with freshly prepared [3,4-bis(benzyloxy)phenyl]lithium provided (1R,2S,3R,4R)-9a (44% yield) and (1S,2S,3R,4R)-9b (15% yield), each as a single diastereomer, together with their diastereomers (9% yield). The relative stereochemistry of (1R,2S,3R,4R)-9a and (1S,2S,3R,4R)-9b was assigned by the analysis of the coupling constants between H-1/H-2 and H-3/H-4 (for (1R,2S,3R,4R)-9a; \textsuperscript{3}J\textsubscript{H1,2} = 4.6 Hz, \textsuperscript{3}J\textsubscript{H3,4} = 6.8 Hz, for (1S,2S,3R,4R)-9b; \textsuperscript{3}J\textsubscript{H1,2} = 7.8 Hz, \textsuperscript{3}J\textsubscript{H3,4} = 9.8 Hz, see the Supplementary Material). TBS deprotection of (1R,2S,3R,4R)-9a and

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**Scheme 2.** Synthesis of 2,5-diaryl-3,4-dimethyltetrahydrofurans from 1,4-diarylbutane-1,4-diols.
Using TBAF in THF gave (1S,2S,3R,4R)-1a and (1S,2S,3R,4R)-1b, in 73% and 71% yields, respectively (for (1R,2S,3R,4R)-1a; 3JH1,2 = 0 Hz, 3JH3,4 = 9.6 Hz, for (1S,2S,3R,4R)-1b; H-1 and H-4 are overlapped and appear as multiplets).

Scheme 3. The synthesis and the direct cyclization of (1R,2S,3R,4R)-1a and (1S,2S,3R,4R)-1b.

To begin with, an acid-catalyzed cyclization reaction of (1R,2S,3R,4R)-1a and (1S,2S,3R,4R)-1b was investigated. Proposely, upon treatment of (1R,2S,3R,4R)-1a and (1S,2S,3R,4R)-1b with an acid, a benzylic carbocation of type C would be chemoselectively generated due to a greater ability of Ar2 bearing two EDGs versus Ar1 to stabilize the carbocation (Scheme 2c). Indeed, when (1R,2S,3R,4R)-1a was simply treated with a catalytic amount of p-TsOH monohydrate in CH2Cl2 at room temperature, (2S,3S,4R,5R)-3a bearing 2,3-syn-3,4-syn-4,5-anti relative stereochemistry was obtained in 89% yield as a single diastereomer. The relative stereochemistry at the 2,3 and 3,4-positions were assigned by analysis of the coupling constants between H-2/H-3 and H-4/H-5; H-2 and H-5 each appeared as a doublet at δ 4.43 (d, 3JH2,3 = 7.2 Hz) and δ 4.41 (d, 3JH4,5 = 6.8 Hz) ppm, respectively. The NOESY experiments supported the assigned relative stereochemistry of (2S,3S,4R,5R)-3a (see the Supplementary Material). The formation of (2S,3S,4R,5R)-3a from (1R,2S,3R,4R)-1a implied that the benzylic carbocation C1 (C1 vs. D1) was chemoselectively generated and underwent stereoselective cyclization through a more favorable intermediate F1 (E1 vs. F1) affording (2S,3S,4R,5R)-3a in good yield with high stereoselectivity (Scheme 4). Under similar reaction conditions, (1S,2S,3R,4R)-1b was readily converted to (2S,3S,4R,5R)-3a as a single isomer in 97% yield (Scheme 3). This observation confirmed that the synthetic process proceeded through chemoselective formation of C1 followed by stereoselective cyclization. It should be noted that (2R,3S,4R,5R)-4a possessing the 2,3-syn-3,4-syn-4,5-anti relative
stereochemistry derived from either formation of carbocation D1 or non-stereoselective cyclization of C1 was not detected in the crude mixture (1H-NMR analysis).

Encouraged by the above results, a racemic mixture of 2 (Ar\textsuperscript{1}/Ar\textsuperscript{2} = tri-/di-EDGs) was prepared and subjected to an acid-catalyzed reaction. On the same basis, it is expected that 2 should give a benzylic carbocation of type D (Scheme 2c) due to a greater ability of Ar\textsuperscript{1} having three EDGs (Ar\textsuperscript{1} vs. Ar\textsuperscript{2}) to stabilize a carbocation intermediate D. Consecutive cyclization of D should give a mixture of 3 and 4. Experimentally, upon treatment of 2 with p-TsOH monohydrate in CH\textsubscript{2}Cl\textsubscript{2} at room temperature, (2R,3R,4S,5S)-4\textsuperscript{b} bearing the 2,3-anti-3,4-syn-4,5-anti relative stereochemistry was obtained in 92% yield as a single diastereomer\textsuperscript{16} while (2R,3R,4S,5R)-3\textsuperscript{b} was not detected (Scheme 5). The results obtained implied that the carbocation intermediate C2 instead of D2 was chemoselectively generated from 2 and underwent stereoselective cyclization to give (2R,3R,4S,5S)-3\textsuperscript{b}. This presumably due to the developing steric interaction between the adjacent methoxy and benzyloxy substituents on the aromatic ring of carbocation intermediate D2. The destabilization effect of MeO group located on the meta position with respect to the forming carbocation D2 should not be excluded.

The study on the acid-catalyzed direct cyclization of 1 and 2 provided the information that the substitution patterns and types of the substituents on the aromatic rings of 1 and 2 were highly important for chemoselective formation of the benzylic carbocation in the first step. Not only an electronic nature but also the steric effect causing by the substituents on the aryl rings plays an important role. In the cyclization process, the inherent stereochemistry presenting in 1 and 2 dictated the stereoselectivity of the reaction providing (2S,3S,4R,5R)-3\textsuperscript{a} and (2R,3R,4S,5S)-3\textsuperscript{b} in good yields and high stereoselectivity.

Finally, (2S,3S,4R,5S)-3\textsuperscript{a} was subjected to hydrogenolysis (H\textsubscript{2}, Pd/C, EtOAc) to provide (2S,3S,4R,5S)-10 in 71% yield as a single isomer (Scheme 6). The spectroscopic data of (2S,3S,4R,5S)-10 {[\alpha]_{D}^{25} +5.7 (c 0.88, CH\textsubscript{2}Cl\textsubscript{2})} are almost identical to those reported for (2,3-anti-3,4-syn-4,5-anti)-5-(4-hydroxyphenyl)-2-(4-hydroxy-3-methoxyphenyl)-3,4-dimethyltetrahydrofuran (11) {[\alpha]_{D}^{21} +3.7 (c 0.54, MeOH)}\textsuperscript{18} isolated from Krameria cystisoides (see the Supplementary Material). Thus, the (2S,3S,4R,5S) absolute configurations presenting in the tetrahydrofuran-core of 11 was then confirmed.
Scheme 5. Acid-catalyzed a direct cyclization of 2.

### Table 1. The spectroscopic data of (2S,3S,4R,5R)-10 and natural compound 11

<table>
<thead>
<tr>
<th>position</th>
<th>(2,3-anti-3,4-syn-4,5-anti)-11</th>
<th>(2S,3S,4R,5R)-10</th>
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<tr>
<td></td>
<td>$\delta_H^b$</td>
<td>$\delta_C^c$</td>
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<tr>
<td>2</td>
<td>4.40 (br d, 6.7)</td>
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<td>2.25 (m)</td>
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<td>4</td>
<td>2.25 (m)</td>
<td>45.65†</td>
</tr>
<tr>
<td>5</td>
<td>4.40 (br d, 6.7)</td>
<td>87.95*</td>
</tr>
<tr>
<td>3-Me</td>
<td>0.95-1.05 (m)</td>
<td>12.95‡</td>
</tr>
<tr>
<td>4-Me</td>
<td>0.95-1.05 (m)</td>
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<tr>
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<tr>
<td>3’</td>
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<tr>
<td>4’</td>
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<td>5’</td>
<td>7.32 (dm, 8.5)</td>
<td>115.48</td>
</tr>
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<td>6’</td>
<td>7.32 (dm, 8.5)</td>
<td>119.95</td>
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<tr>
<td>1”</td>
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<td>-OH</td>
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</table>

*Data were measured in acetone-$d_6$. $\delta_H^b$ (mult., $J$ in Hz) (90 MHz). $\delta_C^c$ (22.5 MHz). $\delta_H^{d,f}$ (mult., $J$ in Hz) (400 MHz). $\delta_C^{e,f}$ (100 MHz). †Unless stated otherwise, the assignment was confirmed on the basis of HSQC and HMBC correlations. *, †, ‡ Similar values within a column may be interchanged.

### Conclusions

In conclusion, the investigation on a direct cyclization of unprotected chiral 1,4-diarylbutane-1,4-diols to access unsymmetrical chiral 2,5-diaryl-3,4-dimethyltetrahydrofurans bearing the 2,3-anti-3,4-syn-4,5-anti relative stereochemistry is reported. Upon treatment with an acid, chiral 1,4-diarylbutane-1,4-diols underwent chemoselective formation of a more stabilized benzylic carbocation followed by stereoselective cyclization leading to chiral furan products in high yields and stereoselectivity in a single operation. Chemoselective generation of the carbocation intermediate was proposed to be governed by the electronic nature and the...
The steric effect of the substituents on the aromatic rings of 1,4-diarylbutane-1,4-diols while stereoselective cyclization of the carbocation was presumably controlled by the inherent stereochemistry of the substrates. The present study represents a practical and an atom-economic process providing useful information applicable for further design asymmetric synthesis of bioactive 2,5-diaryl-3,4-dimethyltetrahydrofurans.

**Experimental Section**

**General.** The $^1$H NMR spectra were recorded on a Bruker-400 (400 MHz) spectrometer in acetone-$d_6$ or CDCl$_3$ using tetramethylsilane as an internal standard. The $^{13}$C NMR spectra were recorded on either a Bruker-400 (100 MHz) or JNM-ECZS (100 MHz) spectrometer in acetone-$d_6$ or CDCl$_3$ using residual non-deuterated solvent peaks as an internal standard. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dichloromethane (CH$_2$Cl$_2$) and ethyl acetate (EtOAc) were distilled over calcium hydride and stored over activated molecular sieves (4 Å). Methanol (MeOH) was distilled over Mg powder. Other common solvents (CH$_2$Cl$_2$, hexanes, and EtOAc) were distilled before use. All glassware including needles and syringes were oven-dried and kept in a desiccator before use. Purification was carried out by column chromatography on silica gel. Weinreb amide (2R,3R)-5 and compound 2 were synthesized according to the literature procedure. The spectroscopic data of (2R,3R,4S,5S)-3b are in agreement with those reported.$^{16}$

**(2R,3R)-1-(4-Methoxyphenyl)-2,3-dimethylpent-4-en-1-one [(2R,3R)-6].** A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with 4-bromo-1-methoxybenzene (398.7 mg, 2.13 mmol) and dry THF (5 mL). The solution was cooled at −78 °C then a solution of n-BuLi (1.6 M in hexanes, 1.3 mL, 2.08 mmol) was added dropwise. After stirring for 10 min, a solution of Weinreb amide (2R,3R)-5 (280 mg, 1.64 mmol) in dry THF (5 mL) was added dropwise at −78 °C. The reaction mixture was stirred and slowly warmed up to room temperature. After stirring at room temperature for 2 h, the reaction mixture was quenched with H$_2$O (15 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. Purification by column chromatography (EtOAc:hexanes, 1:9 v/v) afforded (2R,3R)-6 (245.3 mg, 69% yield) with a 92:8 diastereomeric ratio; a colorless oil. R$_f$ 0.45 (EtOAc:hexanes, 1:9 v/v); [α]$_D^{22}$ −39.8 (c 1.43, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.95 (d, J 8.8 Hz, 2H, ArH), 6.94 (d, J 8.8 Hz, 2H, ArH), 5.75–5.64 (m, 1H, CH), 5.06–4.98 (m, 2H, CHH), 3.87 (s, 3H, OCH$_3$), 3.35–3.25 (m, 1H, CH), 2.68–2.54 (m, 1H, CH), 1.11 (d, J 6.8 Hz, 3H, CH$_3$). $^13$C NMR (100 MHz, CDCl$_3$): δ 203.0 (CO), 163.6 (C), 141.5 (CH), 130.7 (2 × CH), 130.5 (C), 115.1 (CH$_2$), 113.9 (2 × CH), 55.6 (OCH$_3$), 45.3 (CH), 41.3 (CH), 19.2 (CH$_3$), 15.9 (CH$_3$). IR (ATR): $v_{max}$ 1669s, 1597s, 1509m, 1457m, 1253s, 1172s cm$^{-1}$. MS: m/z (%) relative intensity 219 [(M + H)$^+$, 60], 218 (M$^+$, 24), 204 (2), 136 (16), 135 (31). HRMS (ESI-TOF) calcd for C$_{19}$H$_{18}$O$_2$Na [M + Na]$^+$: 241.1204, found: 241.1206.

**(1R,2R,3R)-1-(4-Methoxyphenyl)-2,3-dimethylpent-4-en-1-ol [(1R,2R,3R)-7].** A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with (2R,3R)-6 (231.9 mg, 1.06 mmol) and dry MeOH (8 mL). The solution was cooled at −78 °C and NaBH$_4$ (160.4 mg, 4.25 mmol) was added. The reaction mixture was slowly warmed up to 0 °C over 3 h and the stirring was continued at 0 °C for 1 h. Then it was quenched with H$_2$O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phase was dried over anhydrous Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. Purification by column chromatography (EtOAc:hexanes, 1:4 v/v) provided (1R,2R,3R)-7 (199.2 mg, 85% yield) with a 81:11:8 diastereomeric ratio; a colorless oil. R$_f$ 0.52 (EtOAc:hexanes, 1:4 v/v); [α]$_D^{24}$ +6.8 (c 2.21, CHCl$_3$). $^1$H
NMR (400 MHz, CDCl₃): δ 7.23 (d, J 8.6 Hz, 2H, ArH), 6.87 (d, J 8.6 Hz, 2H, ArH), 5.93–5.81 (m, 1H, CH), 5.16–5.06 (m, 2H, CHH), 4.32 (d, J 9.3 Hz, 1H, CH), 3.81 (s, 3H, OCH₃), 2.89–2.78 (m, 1H, CH), 1.87–1.77 (m, 1H, CH), 1.08 (d, J 7.0 Hz, 3H, CH₃), 0.55 (d, J 7.0 Hz, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 159.2 (C), 140.9 (CH), 136.4 (C), 128.2 (2 × CH), 115.1 (CH₂), 113.9 (2 × CH), 77.1 (CH), 55.4 (OCH₃), 45.3 (CH), 37.6 (CH), 18.6 (CH₃), 11.2 (CH₃). IR (ATR): νₘₐₓ 3431 br, 1611m, 1511s, 1458m, 1246s, 1174s cm⁻¹. MS: m/z (%) relative intensity 220 (M⁺, 7), 203 (100). HRMS (ESI-TOF) calcd for C₁₄H₂₀O₂Na [M + Na⁺]: 243.1361, found: 243.1359.

tert-Butyl([(1R,2R,3R)-1-[4-methoxyphenyl]-2,3-dimethylpent-4-en-1-yl]oxy)dimethylsilane [(1R,2R,3R)-8]. A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with (1R,2R,3R)-7 (dr = 82:11:7) (44.3 mg, 0.20 mmol), imidazole (273.7 mg, 4.0 mmol), and dry CH₂Cl₂ (2.5 mL). To the obtained mixture, a solution of TBSCl (606.2 mg, 4.0 mmol) and dry THF (3.5 mL). The solution was cooled at −78 °C and a solution of an argon inlet, and a rubber septum was charged with 4-bromo-1,2-benzylxybenzene (339.7 mg, 0.92 mmol) was added dropwise. After stirring for 10 min, a solution of the above obtained aldehyde in dry and dry THF (3.5 mL). The solution was cooled at −78 °C and a solution of an argon inlet, and a rubber septum was charged with 4-bromo-1,2-benzylxybenzene (339.7 mg, 0.92 mmol) was added dropwise. After stirring for 10 min, a solution of the above obtained aldehyde in dry and dry THF (3.5 mL). The solution was cooled at −78 °C and a solution of an argon inlet, and a rubber septum was charged with 4-bromo-1,2-benzylxybenzene (339.7 mg, 0.92 mmol) was added dropwise. After stirring for 10 min, a solution of the above obtained aldehyde in dry and dry THF (3.5 mL). The solution was cooled at −78 °C and a solution of an argon inlet, and a rubber septum was charged with 4-bromo-1,2-benzylxybenzene (339.7 mg, 0.92 mmol) was added dropwise. After stirring for 10 min, a solution of the above obtained aldehyde in dry and dry THF (3.5 mL).
Hz, 2H, ArH), 5.14 (s, 4H, 2 × CH₂), 4.97 (dd, J 4.6, 4.6 Hz, 1H, CH), 4.75 (d, J 6.8 Hz, 1H, CH), 4.75 (d, J 6.8 Hz, 1H, CH), 3.99 (d, J 4.4 Hz, 1H, OH), 3.77 (s, 3H, OCH₃), 1.96–1.86 (m, 1H, CH), 1.71–1.62 (m, 1H, CH), 0.97 (d, J 6.9 Hz, 3H, CH₃), 0.90 [s, 9H, SiC(CH₃)₃], 0.79 (d, J 7.0 Hz, 3H, CH₃), 0.09 (s, 3H, CH₃), −0.24 (s, 3H, CH₃). ¹³C NMR (100 MHz, acetone-d₆): δ 159.9 (C), 149.6 (C), 148.6 (C), 140.8 (C), 138.9 (2 × C), 136.7 (C), 129.3 (2 × CH), 129.2 (4 × CH), 128.5 (2 × CH), 128.4 (4 × CH), 120.3 (CH), 115.5 (C), 114.6 (CH), 114.0 (2 × CH), 77.9 (CH), 74.4 (CH), 71.9 (CH), 71.8 (CH), 55.5 (OCH₃), 44.8 (CH), 43.9 (CH), 26.5 (3 × CH₃), 18.9 (C), 14.9 (CH₃), 11.5 (CH₃), −4.1 (CH₃), −4.4 (CH₃).

IR (ATR): vₘₐₓ 3380br, 1610m, 1509s, 1455m, 1248s, 1132m cm⁻¹. MS: m/z (%) relative intensity 347 (18), 319 (2), 251 (100), 176 (26), 91 (61). HRMS (ESI-TOF) calcld for C₉₃H₅₅O₅SiNa [M + Na]^⁺: 649.3325, found: 649.3324.

(1S,2S,3R,4R)-9b; a colorless oil; Rₜ 0.34 (EtOAc:hexanes, 1:9 v/v); [α]D³⁰ +30.2 (c 0.81, CH₂Cl₂). ¹H NMR (400 MHz, acetone-d₆): δ 7.53–7.47 (m, 4H, ArH), 7.40–7.34 (m, 4H, ArH), 7.34–7.27 (m, 4H, ArH), 7.11 (d, J 1.4 Hz, 1H, ArH), 6.99 (d, J 8.2 Hz, 1H, ArH), 6.92 (d, J 8.6 Hz, 2H, ArH), 6.87 (dd, J 1.4, 8.2 Hz, 1H, ArH), 5.15 (s, 4H, 2 × CH₂), 4.99 (d, J 7.8 Hz, 1H, CH), 4.47 (s, 1H, OH), 4.43 (d, J 9.8 Hz, 1H, CH), 3.79 (s, 3H, OCH₃), 2.25–2.15 (m, 1H, CH), 2.09–1.96 (m, 1H, CH), 0.92 [s, 9H, SiC(CH₃)₃], 0.81 (d, J 7.2 Hz, 3H, CH₃), 0.57 (d, J 7.1 Hz, 3H, CH₃), 0.18 (s, 3H, CH₃), −0.24 (s, 3H, CH₃). ¹³C NMR (100 MHz, acetone-d₆): δ 160.2 (C), 150.1 (C), 149.5 (C), 140.9 (C), 139.3 (C), 139.1 (C), 138.3 (C), 129.6 (4 × CH), 129.5 (2 × CH), 129.0 (CH), 128.9 (CH), 128.8 (2 × CH), 128.7 (2 × CH), 121.6 (CH), 115.8 (CH), 115.4 (CH), 114.5 (2 × CH), 79.9 (CH), 77.4 (CH), 72.2 (2 × CH₂), 55.9 (OCH₃), 47.1 (CH), 41.5 (CH), 26.9 (3 × CH₃), 19.3 (C), 17.6 (CH₃), 13.5 (CH₃), −3.6 (CH₃), −3.9 (CH₃). IR (ATR): vₘₐₓ 3379br, 1610m, 1510s, 1455m, 1248s, 1133m cm⁻¹. MS: m/z (%) relative intensity 251 (100), 176 (45), 91 (62). HRMS (ESI-TOF) calcld for C₁₉₃H₅₅O₅SiNa [M + Na]^⁺: 649.3325, found: 649.3328.

(1R,2S,3R,4R)-1-[3,4-Bis(benzzyloxy)phenyl]-4-(4-methoxyphenyl)-2,3-dimethylbutane-1,4-diol [(1R,2S,3R,4R)-1a]. A solution of TBAF (26.7 mg, 0.085 mmol) in THF (1 mL) was added to a solution of (1R,2S,3R,4R)-9a (53.0 mg, 0.085 mmol) in THF (1 mL) at room temperature. After stirring for 3 h, the reaction mixture was quenched with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na₂SO₄. After removal of solvents, the crude product was purified by column chromatography (EtOAc:hexanes, 2:3 v/v) to provide (1R,2S,3R,4R)-1a (37.3 mg, 73% yield) as a single diastereomer; a colorless sticky oil. Rₜ 0.33 (EtOAc:hexanes, 2:3 v/v); [α]D³⁰ +4.9 (c 1.71, CH₂Cl₂). ¹H NMR (400 MHz, acetone-d₆): δ 7.54–7.48 (m, 4H, ArH), 7.40–7.33 (m, 4H, ArH), 7.33–7.29 (m, 2H, ArH), 7.26 (d, J 8.5 Hz, 2H, ArH), 7.20 (s, 1H, ArH), 7.03–6.96 (m, 2H, ArH), 6.88 (d, J 8.6 Hz, 2H, ArH), 5.16 (s, 2H, CH₂), 5.15–5.11 (m, 3H, CH₂ and OH), 5.05 (broad s, 1H, OH), 4.96 (s, 1H, CH), 4.42 (d, J 9.6 Hz, 1H, CH), 3.77 (s, 3H, OCH₃), 2.04–1.98 (m, 1H, CH), 1.97–1.87 (m, 1H, CH), 0.91 (d, J 7.1 Hz, 3H, CH₃), 0.66 (d, J 7.0 Hz, 3H, CH₃). ¹³C NMR (100 MHz, acetone-d₆): δ 159.9 (C), 149.5 (C), 148.5 (C), 140.7 (C), 139.0 (C), 138.9 (C), 138.2 (C), 129.2 (4 × CH), 129.1 (2 × CH), 128.5 (4 × CH), 128.4 (2 × CH), 120.0 (CH), 115.4 (CH), 114.4 (CH), 114.3 (2 × CH), 76.7 (CH), 76.1 (CH), 71.8 (CH₂), 71.7 (CH₂), 55.5 (OCH₃), 47.2 (CH), 45.7 (CH), 18.1 (CH₃), 7.9 (CH₃). IR (ATR): vₘₐₓ 3613br, 3257br, 1613m, 1510s, 1457m, 1243s, 1123m cm⁻¹. MS: m/z (%) relative intensity 360 (4), 268 (3), 165 (2), 161 (74), 137 (1), 91 (100). HRMS (ESI-TOF) calcld for C₃₃H₂₆O₃SiNa [M + Na]^⁺: 535.2460, found: 535.2462.
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Supplementary Material

Copies of $^1$H and $^{13}$C NMR spectra of all compounds as well as NOESY experiments of (2S,3S,4R,5R)-3a and (2S,3S,4R,5R)-10 are available in the Supplementary Material associated with this manuscript in the online version of the text.

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