Leoligin-inspired Synthetic Lignans with Selectivity for Cell-type and Bioactivity Relevant for Cardiovascular Disease

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Experimental Section Chemistry

General Notes

Chemicals

Unless noted otherwise, reactants and reagents were purchased from commercial sources and used without further purification. Dry toluene, CH₂Cl₂, Et₂O, THF and MeOH were obtained from a dispensing system by passing commercial material through a cartridge containing activated alumina (PURESOLV, Innovative Technology), stored under dry nitrogen and then used as such without further drying unless specified. Dry EtOH and DMF were purchased from a commercial source and used without further drying. DMSO was dried by treating commercial material with CaH₂ mesh at 150 °C under argon, followed by distillation under reduced pressure.¹ Deoxygenated and dry THF was obtained by refluxing and distilling pre-dried material (as described above) from sodium and benzophenone under argon.² Zinc dust was activated by treating commercially available zinc dust with aqueous HCl (2 M), followed by thorough washing with water, subsequently with MeOH and dry Et₂O. After drying in vacuo at 60 °C the material was stored under argon.³ Molecular sieves were activated by heating them to 200 °C for approximately 6 h in high vacuum and were then stored under argon.⁴ DIBAL-H in hydrocarbon solutions were reaction-titrated according to a literature procedure, and the content of active DIBAL-H was determined by standard ¹H NMR spectroscopy.⁵ An iodine test was used to check for the presence of oxidant in certain reactions. Therein, KI and starch (1 spatula tip each) was heated in water (approximately 10 mL) until completely dissolved and allowed to cool to room temperature before aliquots (approximately 1 mL) were then combined with a few drops of the solution to be tested.

Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope or an SRS OptiMelt Automated Melting Point System, and are uncorrected. Temperatures are reported in intervals of 0.5 °C.

Aluminum-backed Merck silica gel 60 with fluorescence indicator F₂₅₄ was used for Thin Layer Chromatography (TLC). Spots were visualized under UV light (254 nm) and by staining with cerium ammonium molybdate (CAM) solution (20 g of ammonium pentamolybdate, 0.8 g of cerium(IV) ammonium sulfate, 400 mL of 10 v/v % sulfuric acid) as a general purpose reagent. Alcohols were also visualized with p-anisaldehyde solution (3.5 g p-anisaldehyde, 1.5 mL acetic acid, 5 mL sulfuric acid, 120 mL ethanol), and compounds pertaining double bonds were visualized with potassium permanganate solution (1.5 g potassium permanganate, 10 g potassium carbonate, 1 mL 10 w/w % NaOH, 200 mL water).

Specific rotation was measured using an Anton Parr MCP500 polarimeter and HPLC grade solvents under conditions as specified individually. Values are reported in the form + or - specific rotation (concentration in terms of g / 100 mL, solvent).

Analytical Chromatography-Spectroscopy

Gas Chromatography-Mass Spectroscopy (GC-MS) was used to analyze samples of reaction products with sufficient volatility. The following instruments and columns were used:
Instrument 1: Thermo Scientific Finnigan Focus GC / Quadrupole DSQ II device using a helium flow of 2.0 mL / min, analyzing an m/z range from 50 to 650.

Instrument 2: Thermo Scientific Trace 1300 / ISQ LT Single Quadrupole Mass Spectrometer device using a helium flow of 1.5 mL / min, analyzing an m/z range from 50 to 550.

Column 1: BGB 5 (0.25 µm film; 30 m x 0.25 mm ID)
Column 2: Rxi-5Sil MS (0.25 µm film; 30 m x 0.25 mm ID)
Column 3: TR-5 MS (0.50 µm film; 30 m x 0.25 mm ID)

Temperature gradients are as follows:

Method A: Instrument 1, Column 1:
100 °C (2 min), to 280 °C (15 °C / min)

Method B: Instrument 1, Column 1:
40 °C (2 min), to 60 °C (1 °C / min), to 280 °C (70 °C / min), 280 °C (1 min)

Method C: Instrument 1, Column 1:
100 °C (2 min), to 280 °C (18 °C / min), 280 °C (3 min)

Method D: Instrument 1, Column 1:
100 °C (2 min), to 280 °C (40 °C / min), 280 °C (23 min)

Method E: Instrument 1, Column 1:
100 °C (2 min), to 280 °C (40 °C / min), 280 °C (38 min)

Method F: Instrument 1, Column 1:
100 °C (2 min), to 280 °C (40 °C / min), 280 °C (48 min)

Method G: Instrument 2, Column 2:
100 °C (2 min), to 300 °C (35 °C / min), 300 °C (2 min)

Method H: Instrument 2, Column 3:
40 °C (2 min), to 280 °C (32 °C / min), 280 °C (2 min)

Method I: Instrument 2, Column 3:
100 °C (2 min), to 280 °C (40 °C / min), 280 °C (38 min)

Method J: Instrument 2, Column 3:
100 °C (2 min), to 280 °C (40 °C / min), 280 °C (58 min)

Data is reported in the form retention time; m/z$_1$ (relative intensity in %), m/z$_2$ (relative intensity in %), ... Only signals with m/z ≥ 90 and relative intensity ≥ 15 % are given, except for the signal at 100 % relative intensity which is always given. Also, the molecular ion signal M$^+$ is given regardless of its intensity or m/z; in cases where M$^+$ was not visible due to excessive fragmentation, a characteristic fragment signal is identified instead.

High Pressure Liquid Chromatography (HPLC) was used to determine enantiomeric excess of reaction products, using a Dionex UltiMate 3000 device (RS Diode Array Detector). Chiral separation columns and analysis conditions are specified individually. In all cases, retention times include appropriate guard cartridges containing the same stationary phase as the separation column.

Liquid Chromatography-High Resolution Mass Spectroscopy (LC-HRMS) was used to confirm exact molecular mass of reaction products by their quasi-molecular ions (M$^+$H$^+$ or M$^+$Na$^+$). The following two instruments were used:

Instrument 1: Shimadzu Prominence HPLC device (DGU-20 A3 degassing unit, 2 x LC-20AD binary gradient pump, SIL-20 A auto injector, CTO-20AC column oven, CBM-20A control module, and SPD-M20A diode array detector). Samples were eluted through a Phenomenex Kinetex precolumn (5 µm...
core shell ODS(3) phase; 4 mm x 2 mm ID) at 40 °C under conditions comprising gradients of H₂O / MeOH containing formic acid (0.1 v/v %), and then detected using a Shimadzu IT-TOF-MS by Electrospray Ionization (ESI) or Atmospheric Pressure Chemical Ionization (APCI), as indicated individually. Analyses were performed by E. Rosenberg (CTA, VUT) and L. Czollner (IAS, VUT).

Instrument 2: Agilent 1100/1200 HPLC device (degassing unit, 1200SL binary gradient pump, column thermostat, and CTC Analytics HTC PAL autosampler). Samples were eluted through a silica-based Phenomenex C-18 Security guard cartridge (1.7 µm PD; 2.1 mm ID) at 40 °C under isocratic conditions comprising H₂O containing formic acid (0.1 v/v %) / MeOH containing formic acid (0.1 v/v %) in a ratio of 30 : 70 at a flow rate of 0.5 mL / min, and then detected using an Agilent 6230 LC-TOF-MS equipped with an Agilent Dual AJS ESI source by Electrospray Ionization (ESI). Analyses were performed by L. Czollner (IAS, VUT).

Preparative chromatography

Flash column chromatography was carried out on Merck silica gel 60 (40-63 µm), and separations were performed using a Büchi Sepacore system (dual Pump Module C-605, Pump Manager C-615, Fraction Collector C-660, and UV Monitor C-630 or UV Photometer C-635). Preparative High Pressure Liquid Chromatography (preparative HPLC) was carried out on a Phenomenex Luna reversed-phase column (10 µm C18(2) phase, 100 A; 250 mm x 21.20 mm ID), and separations were performed using a Shimadzu LC-8A device (SIL-10AP autosampler, SPD-20 detector, and FRC-10A fraction collector).

Reaction temperatures were measured externally (electronic thermometer connected to heater-stirrer or low temperature thermometer in case of cryogenic reactions) unless otherwise noted. Partition coefficients (log P values) were calculated using ACD/Labs 12 with LogP Accuracy Extender.

Nuclear Magnetic Resonance (NMR) spectroscopy

NMR spectra were recorded from CDCl₃ or DMSO-d₆ solutions on a Bruker AC 200 (200 MHz proton resonance frequency) or a Bruker Advanced UltraShield (400 MHz) spectrometer (as indicated individually), and chemical shifts are reported in ascending order in ppm relative to the nominal residual solvent signals, i.e. ¹H: δ = 2.50 ppm (DMSO-d₆); ¹³C: δ = 77.16 ppm (CDCl₃), δ = 39.52 ppm (DMSO-d₆). For all ¹H spectra in CDCl₃, however, shifts are reported relative to TMS as internal standard (δ = 0 ppm) due to the interference of aromatic signals of many samples with the residual solvent signal of CDCl₃. For ¹³C spectra, J-modulated (APT) or DEPT-135 pulse sequences were used to aid in the assignment.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ADD</td>
<td>1,1’-(azodicarbonyl)dipiperidine</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>apoAI</td>
<td>apolipoprotein A1</td>
</tr>
<tr>
<td>BAIB</td>
<td>[bis(acetoxy)iodo]benzene ((diacetoxyiodo)benzene)</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>BSA</td>
<td>bovine serum albumin</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
</tbody>
</table>
DEAD diethyl azodicarboxylate
d-(-)-DET (unnatural) (-)-diethyl d-tartrate
DIAD disopropyl azodicarboxylate
DIBAL-H diisobutylaluminum hydride
DIPEA N,N-disopropylethylamine (Hünig’s base)
4-DMAP 4-(dimethylamino)pyridine
DMEM(/F12) Dulbecco’s Modified Eagle Medium (Nutrient Mixture F-12)
DMF dimethylformamide
DMSO dimethylsulfoxide
DPPA diphenyl phosphorazyl azide (diphenyl phosphorazidate)
dppf 1,1’-bis(diphenylphosphino)ferrocene
ECL enhanced chemiluminescence
EDCI N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide
FBS fetal bovine serum
HEPES 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid
INT 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyl-2H-tetrazolium chloride
LDH lactate dehydrogenase
LP light petroleum (boiling range approximately 40 to 60 °C)
Ms mesyl (methanesulfonyl)
MTBE methyl tert-butyl ether (tert-butyl methyl ether)
NAD+ nicotinamide adenine dinucleotide
PDGF(-BB) platelet-derived growth factor (B homodimer)
PMA phorbol 12-myristate 13-acetate
PMSF phenylmethylsulfonyl fluoride
RPMI Roswell Park Memorial Institute
SDS-PAGE sodium dodecyl sulfate-polyacrylamide gel electrophoresis
TBAF tetrabutylammonium fluoride
TBDMSC tert-butyldimethylsilyl
TBHP tert-butyl hydroperoxide
TEA triethylamine
TEMPO 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
THF tetrahydrofuran
TNFα tumor necrosis factor alpha
(V)EC (vascular) endothelial cell (specified vascular where appropriate)
(V)SMC (vascular) smooth muscle cell (specified vascular where appropriate)

Explanation for substrate controlled stereoselective hyroboration

Compound 6 was protected, initially with an acetyl group, to test whether the ester required in the final products could be introduced already at this point. However, what we found was an unsatisfactory diastereoselectivity of 82:18, but in favor of the desired 3,4-cis configuration. Since esterification with angelic acid would lead to a trigonally planar geometry of the resulting ester, it was believed that also in this case the steric demand of the ester would be insufficient to guarantee high
3,4-cis selectivity. Hence, we switched to silyl protecting groups with tetrahedral geometry. Our rational was based on configurational considerations as shown in the schemes below.

We have drawn the substrate molecule in two different configurations and minimized the energy via ChemDraw 3D. The result is in both cases the same. Attack from the side leading to the 3,4-cis product is favored over the attack from the side leading to the 3,4-trans product. Carrying out the corresponding reactions showed that indeed with the bulky TBDMS group enough steric shielding on the bottom face of the molecule was provided to allow 3,4-cis diastereoselective hydroboration (~95:5) with commonly used and bulky 9-borabicyclo(3.3.1)nonane (9-BBN) as reagent. Furthermore, using TIPS, TBDPS, or TBDMS made no significant difference from 95 : 5 and hence TBDMS was eventually chosen as the most economical option.
General Procedure for Grignard Addition

Preparation: a reaction vessel was charged with a stirring bar, aldehyde 2 (1.00 equiv.) and was then evacuated and back-filled with argon using standard Schlenk technique. Dry THF was then added via syringe or canula and the stirred mixture was cooled to -60 °C in a MeOH / liquid N₂ bath, followed by the slow addition of vinylmagnesium bromide solution (1 M in THF, 1.15 equiv.) via syringe or by using an addition funnel while keeping the reaction at this temperature. Reaction progress was monitored by TLC and the reaction was terminated when complete.

Work-up: the mixture was treated as detailed individually below to afford the title compound rac-3.

1-(3,4-Dimethoxyphenyl)prop-2-en-1-ol (rac-3a)

Preparation: according to the General Procedure, 3,4-dimethoxybenzaldehyde (73.1 g, 440.0 mmol, 1.00 equiv.) and THF (600 mL) were used, and vinylmagnesium bromide solution (506.0 mL, 506.0 mmol, 1.15 equiv.) was added over a period of 110 min, after which the mixture was allowed to warm to 10 °C over 2 h.

Work-up: a saturated aqueous NH₄Cl solution (100 mL) was added slowly over 5 min while providing additional cooling to prevent the temperature from rising over +10 °C during the exothermic hydrolysis. To dissolve the magnesium salts, water (450 mL) was added and the mixture was extracted with Et₂O (1 x 500 mL, 5 x 250 mL). The combined organic phases were treated with saturated aqueous NaHCO₃ solution (150 mL) and brine (100 mL), followed by drying with Na₂SO₄. The solution was filtered through a plug of silica (15 g, pre-conditioned with Et₂O) and the solvents were evaporated to afford the title compound rac-3a. This compound is literature-known.⁸

Yield: 85.4 g, 99 %
Appearance: pale yellow oil

1-(4-Fluorophenyl)prop-2-en-1-ol (rac-3b)

Preparation: according to the General Procedure, 4-fluorobenzaldehyde (6.82 g, 55.0 mmol, 1.00 equiv.) and THF (100 mL) were used, and vinylmagnesium bromide solution (63.3 mL, 63.3 mmol, 1.15
equiv.) was added over a period of 30 min, after which the mixture was allowed to warm to -30 °C over 2 h.

**Work-up:** a saturated aqueous NH₄Cl solution (13 mL) was added slowly while providing additional cooling to prevent the temperature from rising over -20 °C during the exothermic hydrolysis. To dissolve the magnesium salts, water (160 mL) was added and the mixture was extracted with Et₂O (1 x 70 mL, 5 x 40 mL). The combined organic phases were treated with saturated aqueous NaHCO₃ solution (20 mL) and brine (13 mL), followed by drying with Na₂SO₄. The solution was filtered through a plug of silica (10 g, pre-conditioned with Et₂O) and the solvents were evaporated at a minimum pressure of 100 mbar to afford the title compound rac-3b. This compound is literature-known.⁹

**Yield:** 8.36 g, > 99 %

**Appearance:** pale yellow oil

### General Procedure for Kinetic Resolution

![Diagram of reaction](image)

**Preparation:** a reaction vessel was charged with racemic alcohol rac-3 (1.00 equiv.) and vinyl acetate (4.00 equiv.), followed by the addition of MTBE and Amano lipase PS (immobilized on diatomite). The suspension was stirred at 40 °C until conversion of the undesired enantiomer (R)-3 to its acetate (R)-Ac-3 was complete, as monitored by chiral HPLC.

**Work-up and purification:** the mixture was treated as detailed individually below to afford the title compound (S)-3a-c.

**(S)-1-(3,4-Dimethoxyphenyl)prop-2-en-1-ol ((S)-3a)**

![Chemical structure of (S)-3a](image)

**Preparation:** according to the General Procedure, starting material rac-3a (85.4 g, 439.7 mmol, 1.0 equiv.), vinyl acetate (151.5 g, 162 mL, 1.76 mol, 4.0 equiv.) and Amano lipase PS (12.82 g, 15 w/w %) were used, and the suspension was stirred mechanically in MTBE (2.4 L) for 45 h.

**Work-up and purification:** the mixture was filtered through a pad of celite 545, rinsed with Et₂O (100 mL) and the solvent were evaporated. Flash column chromatography was then performed (flow rate 50 mL / min, EtOAc / LP), splitting the crude material (in total 98.9 g) into batches for separate chromatographic runs as follows:

- 10.4 g crude: 90 g silica with 9 g precolumn, 15 : 85 isocratically for 30 min, then to 40 : 60 in 80 min.
- 15.0 g crude: 90 g silica with 9 g precolumn, 15 : 85 isocratically for 55 min, then to 40 : 60 in 40 min.
20.5 g crude: 130 g silica, 15 : 85 isocratically for 40 min, then to 25 : 75 in 5 min, then to 55 : 45 in 40 min.
53.0 g crude: 180 g silica 11 : 89 isocratically for 35 min, then 15 : 85 isocratically for 35 min, then to 25 : 75 in 5 min, then to 65 : 35 in 40 min.
This resulted in a pale yellow oil which crystallized upon standing to afford the title compound (S)-3a. This compound is literature-known.\(^8\)

Yield: 34.4 g, 40 % (theoretical maximum yield is 50 %)
Appearance: off-white crystals
Melting range: 51.0 – 53.5 °C; lit.\(^8\) melting range: n/a (compound obtained as a liquid)
R\(_f\) (silica): 0.59 (EtOAc / LP, 2 : 1)
[\(\alpha\)]\(_{D20}\): -13.4 (c 2.00, benzene); lit.\(^8\) [\(\alpha\)]\(_{D}\): -10.8 (c 2.78, benzene)
e.e.: > 98 % (HPLC)

HPLC: 12.1 min ((S)-3a, title compound), 13.5 min ((R)-3a); Diacel CHIRALPAK AS-H, flow rate 1.0 mL / min, \(i\)-PrOH / heptane, 10.0 : 90.0, 25 °C, detection at 235 nm.
GC-MS (EI, 70 eV, Method A): 7.24 min; 194.1 (M\(^+\), 100), 167.1 (17), 165.1 (25), 163.1 (59), 151.1 (29), 139.1 (92), 138.1 (22), 124.0 (18), 91.1 (16).
\(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 2.08 (d, \(^3\)J = 3.1 Hz, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 5.10 – 5.18 (m, 1H), 5.19 (ddd, \(^2\)J = 1.3 Hz, \(^3\)J = 10.2 Hz, \(^4\)J = 1.3 Hz, 1H), 5.34 (ddd, \(^2\)J = 1.4 Hz, \(^3\)J = 17.1 Hz, \(^4\)J = 1.4 Hz, 1H), 6.05 (ddd, \(^3\)J\(_{cis}\) = 10.2 Hz, \(^3\)J\(_{trans}\) = 17.0 Hz, \(^3\)J\(_{vic}\) = 5.9 Hz, 1H), 6.79 – 6.96 (m, 3H).
\(^13\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 55.9, 56.0, 75.2, 109.6, 111.1, 115.0, 118.7, 135.4, 140.4, 148.7, 149.2.

(S)-1-Phenylprop-2-en-1-ol ((S)-3b)

Preparation: according to the General Procedure, commercially available rac-1-phenylprop-2-en-1-ol (9.08 g, 67.7 mmol, 1.0 equiv.), vinyl acetate (23.3 g, 24.9 mL, 271 mmol, 4.0 equiv.) and Amano lipase PS (1.977 g, 22 w/w %) were used, and the suspension was stirred magnetically in MTBE (500 mL) for 23 h.

Work-up and purification: the mixture was filtered through a pad of celite 545, rinsed with Et\(_2\)O (50 mL) and the solvents were evaporated. Flash column chromatography (180 g silica, flow rate 50 mL / min, Et\(_2\)O / LP, 10 : 90 for 23 min, then to 23 : 77 in 13 min, then to 48 : 52 in 14 min) and prolonged evaporation at a minimum pressure of 190 mbar afforded the title compound (S)-3b. This compound is literature-known.\(^8-10\)

Yield: 4.20 g, 46 % (theoretical maximum yield is 50 %)
Appearance: nearly colorless oil
R\(_f\) (silica): 0.36 (Et\(_2\)O / LP, 1 : 3)
[\(\alpha\)]\(_{D20}\): -4.2 (c 1.0, CHCl\(_3\)); lit.\(^9\) [\(\alpha\)]\(_{D}\): -2.5 (c 1.0, CHCl\(_3\)); lit.\(^10\) [\(\alpha\)]\(_{D25}\): -5.9 (c 1.73, benzene)
e.e.: > 98 % (HPLC)
HPLC: 49.0 min ((R)-3b), 52.0 min ((S)-3b, title compound); Diacel CHIRALPAK IA, flow rate 1.0 mL / min, i-PrOH / heptane, 7.0 : 93.0, 25 °C, detection at 220 nm.
GC-MS (EI, 70 eV, Method G): 3.61 min; 134.2 (M⁺, 54), 133.2 (98), 115.1 (36), 107.1 (18), 105.1 (80), 92.1 (69), 91.1 (39).
1H NMR (200 MHz, CDCl₃): δ 2.11 (bs, 1H), 5.16 – 5.26 (m, 2H, H₂), 5.36 (d, ³J = 17.1 Hz, 1H), 5.96 – 6.17 (m, 1H), 7.25 – 7.41 (m, 5H).
13C NMR (50 MHz, CDCl₃): δ 75.5, 115.2, 126.5, 127.9, 128.7, 140.4, 142.7.

(S)-3b, C₉H₉FO 152.17 g mol⁻¹

Preparation: according to the General Procedure, starting material rac-3c (8.36 g, 55.0 mmol, 1.0 equiv.), vinyl acetate (18.9 g, 20.4 mL, 220 mmol, 4.0 equiv.) and Amano lipase PS (1.25 g, 15 w/w %) were used, and the suspension was stirred magnetically in MTBE (300 mL) for 26 h.
Work-up and purification: the mixture was filtered through a pad of celite 545, rinsed with Et₂O (50 mL) and the solvents were evaporated. Flash column chromatography (90 g silica, flow rate 50 mL / min, EtOAc / LP, 1 : 99 to 5 : 95 in 40 min, then to 20 : 80 in 40 min) and prolonged evaporation at a minimum pressure of 170 mbar at 50 °C afforded the title compound (S)-3c. This compound is literature-known.

Yield: 3.34 g, 40 % (theoretical maximum yield is 50 %)
Appearance: nearly colorless oil
Rₜ (silica): 0.40 (EtOAc / LP, 1 : 2)
[α]D²⁰: +5.4 (c 2.74, MeOH); lit. [α]D²⁰: +11.3 (c 0.81, CHCl₃), deviation likely due to different solvent used
e.e.: > 98 % (HPLC)

HPLC: 27.5 min ((R)-3c), 30.1 min ((S)-3c, title compound); Diacel CHIRALPAK AS-H, flow rate 0.9 mL / min, i-PrOH / heptane, 1.5 : 98.5, 25 °C, detection at 254 nm.
GC-MS (EI, 70 eV, Method G): 3.66 min; 152.1 (M⁺, 58), 151.1 (90), 133.1 (47), 125.1 (36), 123.1 (90), 110.1 (56), 109.1 (61), 103.1 (23), 97.1 (100), 96.1 (51), 95.1 (60).
1H NMR (200 MHz, CDCl₃): δ 2.00 (bs, 1H), 5.14 – 5.25 (m, 2H), 5.34 (d, ³J = 17.1 Hz, 1H), 6.02 (ddd, ³Jₕcis = 10.2 Hz, ³Jₕtrans = 16.5 Hz, ³Jₕvic = 5.9 Hz, 1H), 6.97 – 7.11 (m, 2H), 7.28 – 7.40 (m, 2H).
13C NMR (50 MHz, CDCl₃): δ 74.8, 115.5 (d, ³J = 21.4 Hz), 115.5, 128.2 (d, ³J = 8.1 Hz), 138.4 (d, ⁴J = 3.1 Hz), 140.2, 162.4 (d, ⁴J = 245.8 Hz).
**General Procedure** for Propargylation-Epoxidation

![Chemical Structures]

1. NaH, dry DMSO (10 equiv.), dry THF, argon, 0 °C
2. propargyl bromide, 0 °C to r. t.
3. work-up
4. m-CPBA, CH₂Cl₂, 0 °C to r. t.

5. mixture of diastereoisomers

**Preparation:** a reaction vessel was charged with a stirring bar, NaH (approximately 60 % dispersion in mineral oil) and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF and dry DMSO (10.00 equiv.) were then added in this order via syringe or canula and the resulting suspension was cooled to 0 °C in an ice bath. Starting material (S)-3 (1.0 equiv.), as a beforehand-prepared solution in dry THF under argon, was then slowly transferred to the stirred mixture for deprotonation, which after another 15 min of stirring was followed by a solution of propargyl bromide (80 % in toluene), both via syringe or canula. The ice bath was then removed and the reaction continued at room temperature. Progress of this substitution reaction was monitored by TLC, and once complete, the mixture was cooled in an ice bath again and hydrolyzed, while still under argon, by careful addition of aqueous HCl (1 M). For intermediate work-up, most of the THF was then evaporated, followed by the addition of water and extraction with Et₂O (4 x). The combined organic phases were treated with brine, dried with Na₂SO₄, filtered and the solvents were evaporated in a new reaction vessel to give a residue of propargylated intermediate. This residue was then dissolved in CH₂Cl₂ and cooled to 0 °C in an ice bath. m-CPBA (wet, approximately 77 %) was added to the stirred solution in small portions and the reaction was allowed to warm to room temperature. Progress of this epoxidation reaction was monitored by TLC and terminated when complete.

**Work-up:** the mixture was treated as detailed individually below to afford crude compound 5 as a mixture of diastereoisomers to be used directly in the next reaction step.

2-((R)-(3,4-Dimethoxyphenyl)(prop-2-yn-1-yloxy)methyl)oxirane ((αR)-5a)

![Chemical Structures]

**Preparation:** according to the **General Procedure**, a suspension of NaH (15.55 g, 388.7 mmol, 2.20 equiv.) with DMSO (125 mL, 1.76 mol, 10.0 equiv.) in THF (300 mL) was used for deprotonation of starting material (S)-3a (34.32 g, 176.7 mmol, 1.00 equiv.), itself transferred as a solution in THF (300 mL). This was then followed by the addition of propargyl bromide (35.4 mL, 318.1 mmol, 1.8 equiv.). In deviation from the **General Procedure**, additional dry THF (300 mL) was added via syringe immediately thereafter in order to facilitate stirring of the resulting slurry upon propargyl bromide addition. The mixture was then stirred for 13 h.
After work-up of the propargylated intermediate (Rf (silica): 0.74 (EtOAc / LP, 1 : 1)), m-CPBA (178.2 g, 795.2 mmol, 4.5 equiv.) in CH2Cl2 (500 mL) was used for epoxidation, and the mixture was stirred for 17 h.

Work-up: sufficient aqueous Na2SO3 solution was added to destroy residual peroxy acid (iodine test), which required cooling using an ice bath. This was followed by K3PO4 (185 g) as an aqueous solution in water (750 mL) to bring the pT to 8. After extraction with Et2O (1 x 750 mL, 5 x 250 mL), the combined organic phases were treated with brine (250 mL), dried with Na2SO4, filtered and the solvents were evaporated to afford crude compound (αR)-5a as a mixture of diastereoisomers (approximate ratio: major / minor, 53 : 47, by NMR) to be used directly in the next reaction step. This mixture of isomers is literature-known in racemic form.3

Yield: 50.09 g, crude
Appearance: yellow oil
Rf (silica): 0.45 (EtOAc / LP, 1 : 1)

GC-MS (EI, 70 eV, Method C) major isomer: 9.26 min; 248.1 (M+ +, 23), 205.1 (100), 166.1 (45), 165.1 (59), 151.1 (16), 146.1 (15). minor isomer: 9.31 min; 248.1 (M+ +, 20), 205.1 (100), 179.1 (19), 166.1 (53), 165.1 (67), 151.1 (27), 146.1 (19), 138.1 (15), 91.1 (15).

1H NMR (200 MHz, CDCl3) major isomer: δ 2.43 (t, 4J = 2.4 Hz, 1H, C4≡CH), 2.70 (dd, 2J = 5.3 Hz, 3J = 2.6 Hz, 1H, C3-CH), 2.80 (dd, 2J = 5.2 Hz, 3J = 3.9 Hz, 1H, C3-CH), 3.19 (ddd, 3Joxirane = 3.9 Hz, 3Joxirane = 2.6 Hz, 3Jbenzyl = 4.4 Hz, 1H, H3), 3.87 (s, 3H, Ar’-OCH3), 3.89 (s, 3H, Ar’-OCH3*), 3.95 (dd, 2J = 15.8 Hz, 4J = 2.3 Hz, 1H, H5), 4.18 (dd, 2J = 15.7 Hz, 4J = 2.4 Hz, 1H, H5), 4.48 (d, 3J = 4.4 Hz, 1H, H2), 4.61 – 6.94 (m, 3H, Ar’-H). minor isomer: δ 2.42 (t, 4J = 2.3 Hz, 1H, C4≡CH), 2.63 (dd, 2J = 4.9 Hz, 3J = 2.7 Hz, 1H, C3-CH), 2.75 (dd, 2J = 4.8 Hz, 3J = 4.3 Hz, 1H, C3-CH), 3.23 (ddd, 3Joxirane = 4.2 Hz, 3Joxirane = 2.7 Hz, 3Jbenzyl = 6.0 Hz, 1H, H3), 3.87 (s, 3H, Ar’-OCH3), 3.89 (s, 3H, Ar’-OCH3*), 4.04 (dd, 2J = 15.7 Hz, 4J = 2.4 Hz, 1H, H5), 4.23 (d, 3J = 6.0 Hz, 1H, H2), 4.25 (dd, 2J = 15.7 Hz, 4J = 2.4 Hz, 1H, H5), 6.81 – 6.94 (m, 3H, Ar’-H).

13C NMR (50 MHz, CDCl3) major isomer: δ 45.4 (t, C3-C), 54.1 (d, C3), 56.0 (t, C5; overlap with corresponding signal of minor isomer), 56.0 (q, 2 x Ar’-OCH3; overlap with corresponding signal of minor isomer), 74.9 (d, C4≡C; J-mod spectrum shows antipodal signal due to a large 1JCH of approximately 250 Hz), 79.3 (d, C2), 79.5 (s, C4*), 110.4 (d, C2’), 111.0 (d, C5’), 120.5 (d, C6’), 129.4 (s, C1’), 149.3 (s, C4*), 149.4 (s, C3*; signal overlap with C4’ of minor isomer), minor isomer: δ 44.4 (t, C3-C), 55.0 (d, C3), 56.0 (t, C5; overlap with corresponding signal of major isomer), 56.0 (q, Ar’-OCH3; overlap with corresponding signal of major isomer), 56.1 (q, Ar’-OCH3), 74.8 (d, C4≡C; J-mod spectrum shows antipodal signal due to a large 1JCH of approximately 250 Hz), 79.5 (s, C4*), 81.4 (d, C2), 110.0 (d, C2’), 111.1 (d, C5’), 120.1 (d, C6’), 129.6 (s, C1’), 149.4 (s, C4*; signal overlap with C3’ of major isomer), 149.4 (s, C3*).

2-((R)-(4-Fluorophenyl)(prop-2-yn-1-yloxy)methyl)oxirane ((αR)-5b)

Preparation: according to the General Procedure, a suspension of NaH (1.79 g, 44.9 mmol, 2.20 equiv.) with DMSO (14.5 mL, 204 mmol, 10.0 equiv.) in THF (35 mL) was used for deprotonation of starting
material (S)-3b (3.10 g, 20.4 mmol, 1.00 equiv.), itself transferred as a solution in THF (15 mL). This was then followed by the addition of propargyl bromide (4.09 mL, 36.7 mmol, 1.8 equiv.). In deviation from the General Procedure, additional dry THF (10 mL) was added via syringe immediately thereafter in order to facilitate stirring of the resulting slurry upon propargyl bromide addition. The mixture was then stirred for 15 h.

After work-up of the propargylated intermediate (Rf (silica): 0.66 (EtOAc / LP, 1 : 2)), m-CPBA (20.5 g, 91.8 mmol, 4.5 equiv.) in CH2Cl2 (500 mL) was used for epoxidation, and the mixture was stirred for 31 h. In deviation from the General Procedure, more m-CPBA (4.50 g, 20.4 mmol, 1.0 equiv.) was added and stirring was continued for another 14 h.

Work-up: sufficient aqueous Na2SO3 solution was added to destroy residual peroxy acid (iodine test), which required cooling using an ice bath. This was followed by Na3PO4 (30 g) as an aqueous solution in water (90 mL) to bring the pH to 8. After extraction with Et2O (1 x 120 mL, 6 x 80 mL), the combined organic phases were treated with brine (30 mL), dried with Na2SO4, filtered and the solvents were evaporated. In order to remove residual 3-chlorobenzoic acid, the residue was then taken up in a mixture of Et2O / LP (1 : 2, 300 mL), kept at -30 °C overnight and filtered. After evaporation of the solvents, however, this process had to be repeated, this time by taking the residue up in a mixture of Et2O / LP (1 : 3, 100 mL), keeping at -30 °C overnight, followed by filtration. Evaporation of the solvent then afforded crude compound (αR)-5b as a mixture of diastereoisomers (approximate ratio: major / minor, 61 : 39, by NMR) to be used directly in the next reaction step.

Yield: 4.2 g, crude
Appearance: yellow oil
Rf (silica): 0.48 (EtOAc / LP, 1 : 2)

GC-MS (EI, 70 eV, Method C) major isomer: 6.44 min; 206.0 (M+, < 1), 163.0 (87), 133.1 (28), 123.0 (100), 115.1 (44), 109.1 (52), 101.1 (18), 95.1 (33). minor isomer: 6.48 min; 163.0 (M-oxiranyl+, 84), 133.1 (29), 123.0 (100), 115.1 (41), 109.1 (42), 101.1 (18), 95.1 (27), 75.1 (18). M+ not visible.

1H NMR (200 MHz, CDCl3) major isomer: δ 2.44 (t, 4J = 2.2 Hz, 1H), 2.70 (dd, 3J = 5.2 Hz, 2J = 2.6 Hz, 1H), 2.81 (dd, 2J = 5.1 Hz, 3J = 4.0 Hz, 1H), 3.14 – 3.26 (m, 1H), 3.97 (dd, 2J = 15.9 Hz, 4J = 2.4 Hz, 1H), 4.23 (dd, 3J = 15.9 Hz, 4J = 2.4 Hz, 1H), 4.55 (d, 3J = 4.4 Hz, 1H), 7.01 – 7.14 (m, 2H), 7.30 – 7.41 (m, 2H). minor isomer: δ 2.44 (t, 4J = 2.2 Hz, 1H), 2.62 (dd, 2J = 4.8 Hz, 3J = 2.7 Hz, 1H), 2.76 (dd, 2J = 4.8 Hz, 3J = 4.3 Hz, 1H), 3.14 – 3.26 (m, 1H), 4.08 (dd, 2J = 15.8 Hz, 4J = 2.4 Hz, 1H), 4.29 (dd, 2J = 15.7 Hz, 4J = 2.3 Hz, 1H), 4.31 (d, 3J = 6.3 Hz, 1H), 7.01 – 7.14 (m, 2H), 7.30 – 7.41 (m, 2H).

2-((R)-Phenyl(prop-2-yn-1-yloxy)methyl)oxirane ((αR)-5c)

Preparation: according to the General Procedure, a suspension of NaH (2.75 g, 68.7 mmol, 2.20 equiv.) with DMSO (22.2 mL, 312 mmol, 10.0 equiv.) in THF (40 mL) was used for deprotonation of starting material (S)-3c (4.19 g, 31.2 mmol, 1.00 equiv.), itself transferred as a solution in THF (120 mL). This was then followed by the addition of propargyl bromide (6.25 mL, 56.2 mmol, 1.8 equiv.). The mixture was then stirred for 14 h.
After work-up of the propargylated intermediate ($R_\text{f}$ (silica): 0.75 (Et$_2$O / LP, 1 : 10)), m-CPBA (31.47 g, 140.4 mmol, 4.5 equiv.) in CH$_2$Cl$_2$ (57 mL) was used for epoxidation, and the mixture was stirred for 22 h.

Work-up: sufficient aqueous Na$_2$SO$_3$ solution was added to destroy residual peroxy acid (iodine test), which required cooling using an ice bath. This was followed by Na$_3$PO$_4$ as an aqueous solution in water (250 mL) to bring the pH to 9. After extraction with Et$_2$O (5 x 100 mL, 1 x 170 mL), the combined organic phases were treated with brine (100 mL), dried with Na$_2$SO$_4$, filtered and the solvents were evaporated.

In order to remove residual 3-chlorobenzoic acid, the residue was then taken up in Et$_2$O, filtered, the filtrate diluted with Et$_2$O (total volume 200 mL) and treated with a saturated aqueous solution of Na$_3$PO$_4$ (2 x 50 mL). After evaporation of the organic phase, however, this process had to be repeated, this time by taking the residue up in a mixture of Et$_2$O / LP (3 : 5), keeping at -30 °C overnight, followed by filtration. Evaporation of the solvent then afforded crude compound ($\alpha$R)-5c as a mixture of diastereoisomers (approximate ratio: major / minor, 60 : 40, by NMR) to be used directly in the next reaction step. This mixture of isomers is literature-known in racemic form.

Yield: 7.0 g, crude
Appearance: yellow oil
$R_\text{f}$ (silica): 0.53 (Et$_2$O / LP, 1 : 3)

GC-MS (EI, 70 eV, Method C) major isomer: 6.46 min; 145.1 (M-oxiranyl$^+$, 100), 117.1 (15), 115.1 (53), 105.1 (80), 91.1 (60), 77.1 (71), 65.1 (17), 51.1 (45). M$^+$ not visible. minor isomer: 6.52 min; 145.1 (M-oxiranyl$^+$, 100), 105.1 (67), 77.1 (55), 65.1 (17), 51.1 (45). M$^+$ not visible.

$^1$H NMR (200 MHz, CDCl$_3$) major isomer: δ 2.43 (t, $^4$J = 2.4 Hz, 1H), 2.72 – 2.78 (m, 1H), 2.81 (dd, $^2$J = 5.2 Hz, $^3$J = 4.0 Hz, 1H), 3.16 – 3.29 (m, 1H), 3.98 (dd, $^2$J = 15.7 Hz, $^4$J = 15.8 Hz, 1H), 4.23 (dd, $^2$J = 15.7 Hz, $^4$J = 2.4 Hz, 1H), 4.57 (d, $^3$J = 4.3 Hz, 1H), 7.33 – 7.41 (m, 5H). minor isomer: δ 2.43 (t, $^4$J = 2.4 Hz, 1H), 2.64 (dd, $^2$J = 4.8 Hz, $^3$J = 2.8 Hz, 1H), 2.72 – 2.78 (m, 1H), 3.16 – 3.29 (m, 1H), 4.09 (dd, $^2$J = 15.7 Hz, $^4$J = 2.4 Hz, 1H), 4.29 (d, $^3$J = 6.5 Hz, 1H), 4.29 (dd, $^2$J = 15.7 Hz, $^4$J = 2.4 Hz, 1H), 7.33 – 7.41 (m, 5H).

**General Procedure for Stereoconvergent Radical Cyclization**

In this section, a crude mixture of diastereoisomers 5 from the previous propargylation-epoxidation sequence was used. Molar amounts of 5 are thus based on complete-conversion calculations in the propargylation-epoxidation step. However, masses of 5 correspond to the actual gross weight of starting material as used. Yields are calculated over all three steps (propargylation, epoxidation and cyclization).

**Preparation:** a reaction vessel was charged with a stirring bar, activated zinc dust (7.0 equiv.) and bis(cyclopentadienyl)titanium(IV) dichloride (2.5 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry and deoxygenated THF was added to this via syringe or canula, and the resulting suspension was stirred vigorously at room temperature for 1 h to give a green
solution of bis(cyclopentadienyl)titanium(III) chloride, before unconverted residual zinc was allowed to settle for 5 to 10 min.

Meanwhile, a second reaction vessel was charged with a stirring bar, crude starting material 5 (1.0 equiv.) and then evacuated and back-filled with argon, followed by the addition of dry and deoxygenated THF via syringe or canula. Using the canula, the bis(cyclopentadienyl) titanium(III) chloride solution, as prepared above, was then added slowly while stirring the starting material solution at a high rate at room temperature. Reaction progress was monitored by TLC and the reaction terminated when complete.

Work-up and purification: the mixture was treated as detailed individually below to afford the title compounds 6a-c.

((2S,3R)-2-(3,4-Dimethoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methanol (6a)

Preparation: according to the General Procedure, activated zinc dust (79.8 g, 1.22 mol, 7.0 equiv.), bis(cyclopentadienyl) titanium(IV) dichloride (108.6 g, 436.1 mmol, 2.5 equiv.), and THF (2.5 L) were used for the preparation of bis(cyclopentadienyl) titanium(III) chloride, which was added to crude starting material (αR)-5a (49.42 g, 174.3 mmol, 1.0 equiv.) in THF (1.2 L) over a period of 3 h, followed by stirring at room temperature for another 75 min.

Work-up and purification: H₂SO₄ (10 %, 1 L) was added carefully and most of the THF was evaporated at a minimum pressure of 150 mbar at 40 °C. Following repeated extraction with Et₂O, the combined organic phases were treated with saturated aqueous NaHCO₃ solution (500 mL), brine (250 mL), dried with Na₂SO₄, filtered and the solvents were evaporated. Flash column chromatography of the entire crude material in two sequential runs (first run: 180 g silica, flow rate 40 mL / min, EtOAc / LP, 25 : 75 to 50 : 50 in 45 min, then to 100 : 0 in 3 h; second run: 90 g silica, flow rate 40 mL / min, EtOAc / LP, 15 : 85 to 50 : 50 in 45 min, then to 100 : 0 in 3 h) afforded the title compound 6a. This compound is literature-known in racemic form.

Yield: 8.62 g, 20 % (over 3 steps from (S)-3a)
Appearance: brown oil
Rᵣ (silica): 0.19 (EtOAc / heptane, 1 : 1)
\([\alpha]_{D}^{50}\): +21.4 (c 2.07, MeOH)

GC-MS (EI, 70 eV, Method C): 10.37 min; 250.1 (M⁺, 71), 219.1 (21), 167.1 (62), 166.1 (26), 165.1 (40), 152.1 (20), 151.1 (65), 139.1 (100), 124.1 (21).

¹H NMR (200 MHz, CDCl₃): δ 1.63 (bs, 1H), 2.70 – 2.86 (m, 1H), 3.62 – 3.86 (m, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 4.42 (ddddd, 2J = 13.3 Hz, 4Jtrans-allyl = 2.2 Hz*, 4Jcis-allyl = 4.3 Hz*, 1H), 4.56 – 4.69 (m, 1H), 4.79 (d, 3J = 7.5 Hz), 5.02 – 5.16 (m, 2H), 6.79 – 6.98 (m, 3H).

¹³C NMR (50 MHz, CDCl₃): δ 54.0, 55.98, 56.00, 62.0, 71.5, 83.5, 105.1, 109.4, 111.0, 119.0, 133.6, 148.9, 149.0, 149.3.
((2S,3R)-2-(4-Fluorophenyl)-4-methylenetetrahydrofuran-3-yl)methanol (6b)

Preparation: according to the General Procedure, activated zinc dust (9.3 g, 143 mmol, 7.0 equiv.), bis(cyclopentadienyl)titanium(IV) dichloride (12.7 g, 51.0 mmol, 2.5 equiv.), and THF (275 mL) were used for the preparation of bis(cyclopentadienyl)titanium(III) chloride, which was added to crude starting material (αR)-5b (4.20 g, 20.4 mmol, 1.0 equiv.) in THF (150 mL) over a period of 30 min, followed by stirring at room temperature for another 2 h.

Work-up and purification: H₂SO₄ (10 %, 115 mL) was added carefully while the mixture was cooled in an ice bath, and most of the THF was evaporated at a minimum pressure of 160 mbar at 50 °C. Following repeated extraction with Et₂O, the combined organic phases were treated with saturated aqueous NaHCO₃ solution (120 mL), brine (120 mL), dried with Na₂SO₄, filtered and the solvents were evaporated. Flash column chromatography in two sequential runs (first run: 90 g silica, flow rate 40 mL / min, EtOAc / LP, 0 : 100 to 30 : 70 in 2 h; second run: 90 g silica, flow rate 40 mL / min, CH₂Cl₂ / LP, 60 : 40 to 100 : 0 in 40 min, then MeOH / CH₂Cl₂, 10 : 90) afforded the title compound 6b.

Yield: 1.10 g, 26 % (over 3 steps from (S)-3b)

Appearance: off-white crystals

Melting range: 73.0 – 76.0 °C

Rᵣ (silica): 0.36 (EtOAc / heptane, 1 : 1)

[α]D²⁵: +7.7 (c 0.96, MeOH)

GC-MS (EI, 70 eV, Method C): 7.68 min; 208.1 (M⁺, 7), 190.1 (16), 146.1 (20), 133.1 (16), 125.0 (100), 123.1 (33), 122.1 (24), 109.1 (36), 97.1 (45), 95.1 (28).

¹H NMR (200 MHz, CDCl₃): δ 1.65 (bs), 2.67 – 2.83 (m, 1H), 3.72 (dd, ²J = 11.3 Hz, ³J = 4.8 Hz, 1H), 3.87 (dd, ²J = 11.3 Hz, ³J = 5.6 Hz, 1H), 4.42 (ddd, ²J = 13.4 Hz, ³J_C₆-allyl = 2.3 Hz*, ⁴J_C₆-allyl = 4.5*, 1H), 4.55 – 4.67 (m, 1H), 4.85 (d, ³J = 7.2 Hz, 1H), 5.04 – 5.16 (m, 2H), 6.97 – 7.11 (m, 2H), 7.30 – 7.43 (m, 2H).

¹³C NMR (50 MHz, CDCl₃): δ 54.2, 62.0, 71.5, 82.9, 105.4, 115.5 (d, ²J_C₆ = 21.4 Hz), 128.1 (d, ³J_C₆ = 8.1 Hz), 137.1 (d, ⁴J_C₆ = 3.1 Hz), 148.6, 162.5 (d, ¹J_C₆ = 245.9 Hz).

((2S,3R)-4-Methylene-2-phenyltetrahydrofuran-3-yl)methanol (6c)

Preparation: according to the General Procedure, activated zinc dust (14.4 g, 218 mmol, 7.0 equiv.), bis(cyclopentadienyl)titanium(IV) dichloride (19.4 g, 78.0 mmol, 2.5 equiv.), and THF (600 mL) were used for the preparation of bis(cyclopentadienyl)titanium(III) chloride, which was added to crude starting material (αR)-5c (6.96 g, 31.2 mmol, 1.0 equiv.) in THF (200 mL) over a period of 2 h, followed by stirring at room temperature for another 90 min.
Work-up and purification: H$_2$SO$_4$ (10 %, 400 mL) was added carefully and most of the THF was evaporated at a minimum pressure of 140 mbar. Following repeated extraction with Et$_2$O, the combined organic phases were treated with saturated aqueous NaHCO$_3$ solution (80 mL), brine (50 mL), dried with Na$_2$SO$_4$, filtered and the solvents were evaporated. Flash column chromatography (90 g silica, flow rate 40 mL / min, EtOAc / LP, 10 : 90 to 30 : 70 in 60 min), which was re-applied to impure fractions obtained in the first chromatographic run, afforded the title compound 6c. This compound is literature-known in racemic form.$^3$

Yield: 2.02 g, 34 % (over 3 steps from (S)-3c)
Appearance: brown oil
$R_f$ (silica): 0.38 (EtOAc / heptane, 1 : 1)
$[\alpha]_{D}^{25}$: +6.3 (c 0.60, MeOH)

GC-MS (EI, 70 eV, Method C): 7.60 min; 190.1 (M$^+$, 23), 172.1 (20), 129.1 (18), 128.1 (21), 115.1 (18), 107.1 (100), 105.1 (33), 104.1 (26), 91.1 (34).

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.63 (bs, 1H), 2.72 – 2.86 (m, 1H), 3.74 (dd, $^2J = 11.2$ Hz, $^3J = 4.8$ Hz, 1H), 3.88 (dd, $^2J = 11.3$ Hz, $^3J = 5.6$ Hz, 1H), 4.44 (ddd, $^2J = 13.4$ Hz, $^3J_{cis-allyl} = 2.2$ Hz$^*$, $^4J_{trans-allyl} = 4.5$ Hz$^*$, 1H), 4.57 – 4.69 (m, 1H), 4.87 (d, $^3J = 7.1$ Hz, 1H), 5.04 – 5.09 (m, 1H), 5.09 – 5.13 (m, 1H), 7.25 – 7.43 (m, 5H).

$^{13}$C NMR (50 MHz): $\delta$ 54.2, 62.1, 71.5, 83.5, 105.2, 126.4, 127.9, 128.6, 141.3, 148.8.

**General Procedure** for Silyl Protection

Preparation: a reaction vessel was charged with a stirring bar, starting material 6 (1.00 equiv.), imidazole (2.10 equiv.) and 4-DMAP (5 mol %); it was then evacuated and back-filled with argon using standard Schlenk technique. After adding dry DMF via syringe, a solution of TBDMSCl (3 M in THF) was added dropwise to the stirred mixture, also via syringe, and reaction progress was monitored by TLC and terminated when complete.

Work-up and purification: the mixture was treated as detailed individually below to afford crude compound 8a-c to be used directly in the next reaction step.

tert-Butyl(((2S,3R)-2-(3,4-dimethoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methoxy)dimethylsilane (8a)

8a, C$_{20}$H$_{32}$O$_2$Si
364.55 g mol$^{-1}$
Preparation: According to the General Procedure, starting material 6a (1.723 g, 6.885 mmol, 1.00 equiv.), imidazole (984 mg, 14.459 mmol, 2.10 equiv.), 4-DMAP (42 mg, 0.344 mmol, 5 mol %), TBDMSCl solution (3.14 mL, 9.42 mmol, 1.37 equiv.) and DMF (40 mL) were used, and the mixture was stirred at room temperature for 12.5 h.

Work-up and purification: Et$_2$O (100 mL) was added, followed by a saturated aqueous solution of NH$_4$Cl (40 mL). The layers were separated, the aqueous phase was extracted with Et$_2$O (3 x 50 mL), the combined organic phases were treated with a saturated aqueous solution of NaHCO$_3$ (25 mL), brine (25 mL), dried with Na$_2$SO$_4$, filtered and the solvents were evaporated to afford crude compound 8a to be used directly in the next reaction step.

Yield: 2.63 g, crude
Appearance: pale brown oil
$R_t$ (silica): 0.69 (EtOAc / LP, 2 : 5)

GC-MS (EI, 70 eV, Method C): 11.49 min; 364.2 (M$^+$, 5), 232.1 (36), 215.1 (41), 165.0 (42), 151.1 (36), 141.1 (22), 73.0 (100).

$^1$H NMR (200 MHz, CDCl$_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 2.71 – 2.85 (m, 1H), 3.66 – 3.77 (m, 2H), 3.87 (s, 3H), 4.34 – 4.47 (m, 1H), 4.50 – 4.62 (m, 1H), 4.89 (d, $^3$$J$ = 6.3 Hz), 4.99 – 5.06 (m, 2H), 6.78 – 6.94 (m, 3H).

 tert-Butyl(((2S,3R)-2-(4-fluorophenyl)-4-methylenetetrahydrofuran-3-yl)methoxy)dimethylsilane (8b)

Preparation: According to the General Procedure, starting material 6b (1.10 g, 5.28 mmol, 1.00 equiv.), imidazole (755 mg, 11.09 mmol, 2.10 equiv.), 4-DMAP (32.3 mg, 0.26 mmol, 5 mol %), TBDMSCl solution (2.41 mL, 7.24 mmol, 1.37 equiv.) and DMF (33.0 mL) were used, and the mixture was stirred at room temperature for 16 h.

Work-up and purification: Et$_2$O (80 mL) was added, followed by a saturated aqueous solution of NH$_4$Cl (40 mL). The layers were separated, the organic phase was treated with a saturated aqueous solution of NaHCO$_3$ (40 mL), brine (40 mL), dried with Na$_2$SO$_4$, filtered and the solvents were evaporated to afford crude compound 8b to be used directly in the next reaction step.

Yield: 1.91 g, crude
Appearance: pale brown oil
$R_t$ (silica): 0.74 (EtOAc / heptane, 1 : 3)

GC-MS (EI, 70 eV, Method C): 9.27 min; 190.1 (elimination of TBDMSO and H from M$^+$, 5), 161.1 (24), 146.1 (15), 123.0 (36), 109.0 (37), 101.0 (15), 73.0 (100). M$^+$ not visible.

$^1$H NMR (200 MHz, CDCl$_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 2.68 – 2.84 (m, 1H), 3.69 – 3.78 (m, 2H), 4.35 – 4.47 (m, 1H), 4.49 – 4.62 (m, 1H), 4.89 (d, $^3$$J$ = 6.2 Hz, 1H), 4.98 – 5.07 (m, 2H), 6.95 – 7.10 (m, 2H), 7.26 – 7.41 (m, 2H).

 tert-Butyldimethyl(((2S,3R)-4-methylene-2-phenyltetrahydrofuran-3-yl)methoxy)silane (8c)
Preparation: According to the General Procedure, starting material 6c (979 mg, 5.10 mmol, 1.00 equiv.), imidazole (730 mg, 10.66 mmol, 2.10 equiv.), 4-DMAP (33 mg, 0.25 mmol, 5 mol %), TBDMSCl solution (3.2 mL, 9.6 mmol, 1.9 equiv.) and DMF (35 mL) were used, and the mixture was stirred at room temperature for 14 h.

Work-up and purification: Et₂O (70 mL) was added, followed by a saturated aqueous solution of NH₄Cl (30 mL). The layers were separated, the aqueous phase was extracted with Et₂O (3 x 50 mL), the combined organic phases treated with a saturated aqueous solution of Na₂CO₃ (15 mL), brine (15 mL), dried with Na₂SO₄, filtered and the solvents were evaporated to afford crude compound 8c to be used directly in the next reaction step.

Yield: 1.92 g, crude
Appearance: pale brown oil
Rf (silica): 0.40 (EtOAc / LP, 1 : 20)

GC-MS (EI, 70 eV, Method C): 9.29 min; 304.0 (M⁺, < 1), 247.1 (25), 199.1 (32), 172.1 (33), 155.1 (100), 143.1 (60), 141.1 (26), 129.1 (17), 128.1 (28), 115.1 (17), 105.1 (40), 91.1 (23).

¹H NMR (200 MHz, CDCl₃): δ 0.04 (s, 6H), 0.88 (s, 9H), 2.74 – 2.87 (m, 1H), 3.70 – 3.77 (m, 2H), 4.43 (ddd, 2J = 13.1 Hz, 4Jciss-allyl = 2.3 Hz*, 4Jtrans-allyl = 4.4 Hz*, 1H), 4.52 – 4.63 (m, 1H), 4.93 (d, 3J = 6.0 Hz, 1H), 4.99 – 5.05 (m, 2H), 7.24 – 7.41 (m, 5H).

General Outline for 3-(Hydroxymethyl)tetrahydrofuran-type Lignans

In this section, crude starting material 8 from the previous silyl protection was used. Molar amounts of 8 are thus based on complete-conversion calculations in the protection step. However, masses of 8 correspond to the actual gross weight of starting material as used. Yields are calculated over all four steps (protection, hydroboration, coupling and deprotection).

All compounds of generic structure 7 in this section were prepared according to the General Outline above, and are arranged such that compounds with the same R¹ are grouped together. However, certain variations exist with respect to the experimental details, and a single general procedure is therefore not readily stated in more detail. Thus, for the Preparation of any particular compound, the experimental details are either given in full, or the reader is referred to an analogous procedure already described for a compound in this section. Generally, reaction progress was monitored by TLC and the reaction was terminated when complete or when no further conversion was observed.

Details for Work-up and purification are given for each case individually to afford compounds of structure 7.
((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methanol (dimethylariciresinol, leoligin alcohol, 7a)

Preparation: a reaction vessel was charged with a stirring bar and crude starting material 8a (2.51 g, 6.88 mmol, 1.0 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 20.7 mL, 10.3 mmol, 1.5 equiv.) was added via syringe, the reaction was stirred for 16.5 h at 40 °C and then allowed to cool to room temperature. Following this, a degassed aqueous solution of NaOH (2M, 20 mL) was added cautiously and stirring was continued for another 15 min. 4-Iodoveratrole (2.36 g, 8.95 mmol, 1.30 equiv.) and Pd(dppf)Cl2.CH2Cl2 (161 mg, 0.198 mmol, 2.9 mol %) were then added, and the resulting biphasic mixture was stirred vigorously at room temperature for 25 h. Et2O (200 mL) and brine (50 mL) were then added, the layers were separated, the aqueous phase was extracted with Et2O (4 x 50 mL), and the combined organic phases were dried with Na2SO4 and filtered into a new reaction vessel. From there, the solvent was evaporated, a stirring bar was added to the residue and the vessel was evacuated and back-filled with argon. For deprotection, a solution of TBAF (1.0 M in THF, 8.25 mL, 8.25 mmol, 1.2 equiv.) was added via syringe and the mixture was finally stirred for 18 h at room temperature.

Work-up and purification: Et2O (200 mL) and brine (50 mL) was added, the layers were separated and the aqueous phase was extracted with Et2O (4 x 50 mL) and EtOAc (2 x 50 mL). The combined organic phases were dried with Na2SO4, filtered and the solvents were evaporated. Flash column chromatography of the entire crude material in two sequential runs (first run: 90 g silica with 9 g pre-column, flow rate 40 mL / min, EtOAc / LP, 30 : 70 for 3 min, then to 100 : 0 in 60 min; second run: 90 g silica, flow rate 40 mL / min, EtOAc / LP, 45 : 55 to 85 : 15 in 60 min) afforded the title compound 7a.

Dimethylariciresinol is a literature-known natural compound.11-12

Yield: 1.04 g, 39 % (over 4 steps from unprotected alcohol 6a)

Appearance: slightly colored oil

\[
R_t (\text{silica}) = 0.43 \text{ (EtOAc)}
\]

\[
[\alpha]_D^{20} = +19.2 \text{ (c 1.45, MeOH); lit.}^{11} [\alpha]_D^{23}: +19.4 \text{ (c 0.6, CHCl}_3\text{)}
\]

LC-HRMS (ESI): calculated for M+Na\textsuperscript{+}: 411.1778, found: 411.1783, \Delta: 1.22 ppm

\[
\log P_{\text{calc}} = 3.18 \pm 0.56
\]

\[^1\text{H} \text{ NMR (200 MHz, CDCl}_3\text{): } \delta 1.52 (\text{bs, 1H}), 2.42 (\text{quint, } J = 6.9 \text{ Hz, 1H}), 2.56 (\text{dd, } J = 12.7 \text{ Hz, 3J = 10.4 Hz, 1H}), 2.66 - 2.85 (\text{m, 1H}), 2.94 (\text{dd, } J = 12.8 \text{ Hz, 3J = 4.7 Hz, 1H}), 3.73 - 3.98 (\text{m, 2H}), 3.76 (\text{dd, } J = 8.5 \text{ Hz, 3J = 5.9 Hz, 1H}), 3.87 (\text{s, 9H}), 3.88 (\text{s, 3H}), 4.07 (\text{dd, } J = 8.5 \text{ Hz, 3J = 6.4 Hz, 1H}), 4.81 (\text{d, } J = 6.5 \text{ Hz, 1H}), 6.70 - 6.81 (\text{m, 3H}), 6.81 - 6.91 (\text{m, 3H})\]

\[^{13}\text{C} \text{ NMR (50 MHz, CDCl}_3\text{): } \delta 33.4, 42.5, 52.7, 56.1, 61.1, 73.1, 82.9, 109.1, 111.1, 111.4, 112.0, 118.2, 120.6, 133.1, 135.5, 147.6, 148.5, 149.1, 149.2.\]
Preparation: a reaction vessel was charged with a stirring bar and crude starting material 8a (715.9 mg, 1.964 mmol), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 5.89 mL, 2.95 mmol) was added via syringe, the reaction was stirred for 21 h at 40 °C and then allowed to cool to room temperature. Water (35 µL, 2.0 mmol) was subsequently added and stirring was continued for 2 h to decompose excess 9-BBN. This mixture was then purged by bubbling argon into the solution through a needle, and dry and deoxygenated THF was added to produce a total volume of 10.0 mL, i.e. a 0.196 M solution of borylated intermediate, thus allowing the use of aliquots for subsequent coupling.

An aliquot (0.97 mL, 0.19 mmol, 1.0 equiv.) of this solution was transferred via syringe to a separate vessel which had been charged with a stirring bar, 1-bromo-4-((tert-butyl)benzene (52.6 mg, 0.247 mmol, 1.3 equiv.), Pd(dppf)Cl₂.CH₂Cl₂ (3.9 mg, 4.8 µmol, 2.5 mol %) and Cs₂CO₃ (310 mg, 0.950 mmol, 5.0 equiv.) under argon and was stirred for 36 h at room temperature. Following this, MgSO₄ (23 mg, 0.19 mmol, 1.0 equiv.) was added and stirring was continued for 1.5 h to remove residual water. For deprotection, a solution of TBAF (1.0 M in THF, 0.32 mL, 0.32 mmol, 1.7 equiv.) was added via syringe and the mixture was finally stirred for 32 h at room temperature.

Work-up and purification: the heterogeneous reaction content was filtered and rinsed with CH₂Cl₂ (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc in LP, 20 : 80 to 70 : 30 in 30 min) afforded the title compound 7b.

Yield: 49.1 mg, 67 % (over 4 steps from unprotected alcohol 6a)

Appearance: light-brown oil

Rₜ (silica): 0.76 (EtOAc)

[α]D²⁵: +12.0 (c 4.91, MeOH)


(log P)calc: 5.13 ± 0.55

¹H NMR (200 MHz, CDCl₃): δ 1.31 (s, 9H), 1.68 (bs, 1H), 2.40 (quint, ³J = 6.7 Hz, 1H), 2.59 (dd, ⁴J = 12.5 Hz, ³J = 9.8 Hz, 1H), 2.67 – 2.86 (m, 1H), 2.92 (dd, ³J = 12.6 Hz, ⁴J = 4.8 Hz, 1H), 3.69 – 3.98 (m, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.08 (dd, ³J = 8.5 Hz, ³J = 6.4 Hz, 1H), 4.83 (d, ³J = 6.2 Hz, 1H), 6.78 – 6.94 (m, 3H), 7.12 (d, ³J = 8.2 Hz, 2H), 7.31 (d, ³J = 8.2 Hz, 2H).

¹³C NMR (50 MHz, CDCl₃): δ 31.5, 33.1, 34.5, 42.2, 52.5, 56.00, 56.03, 61.0, 73.2, 82.9, 109.0, 111.1, 118.1, 125.5, 128.4, 135.7, 137.4, 148.4, 149.1 (signal overlap).
Preparation: a reaction vessel was charged with a stirring bar and crude starting material 8b (169.3 mg, 0.467 mmol), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 1.40 mL, 0.70 mmol) was added via syringe, the reaction was stirred for 19 h at 40 °C and then allowed to cool to room temperature. Water (9 µL, 0.5 mmol) was subsequently added and stirring was continued for 15 min to decompose excess 9-BBN. This mixture was then purged by bubbling argon into the solution through a needle, and dry and deoxygenated THF was added to produce a total volume of 2.7 mL, i.e. a 0.173 M solution of borylated intermediate, thus allowing the use of aliquots for subsequent coupling.

An aliquot (0.90 mL, 0.156 mmol, 1.0 equiv.) of this solution was transferred via syringe to a separate vessel which had been charged with a stirring bar, 4-iodoveratrole (53.5 mg, 0.202 mmol, 1.3 equiv.), Pd(dppf)Cl₂·CH₂Cl₂ (3.2 mg, 3.9 µmol, 2.5 mol %) and Cs₂CO₃ (254 mg, 0.779 mmol, 5.0 equiv.) under argon and was stirred for 19.5 h at room temperature. Following this, MgSO₄ (19 mg, 0.16 mmol, 1.0 equiv.) was added and stirring was continued for 1.5 h to remove residual water. For deprotection, a solution of TBAF (1.0 M in THF, 0.26 mL, 0.26 mmol, 1.7 equiv.) was added via syringe and the mixture was finally stirred for 21 h at room temperature.

Work-up and purification: the heterogeneous reaction content was filtered and rinsed with CH₂Cl₂ (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 25 : 75 to 70 : 30 in 40 min) afforded the title compound 7c. Yield: 31.5 mg, 58 % (over 4 steps from unprotected alcohol 6b)

Appearance: slightly colored oil

Rₙ (silica): 0.60 (EtOAc)

[α]D: +10.4 (c 0.69, MeOH)

LC-HRMS (APCI): calculated for M+H⁺: 347.1653, found: 347.1668, Δ: 4.32 ppm

(log P)calc: 3.49 ± 0.60

¹H NMR (200 MHz, CDCl₃): δ 1.46 (bs, 1H), 2.38 (quint, 3J = 6.8 Hz, 1H), 2.56 (dd, 2J = 12.6 Hz, 3J = 10.2 Hz, 1H), 2.65 – 2.83 (m, 1H), 2.92 (dd, 2J = 12.7 Hz, 3J = 4.7 Hz, 1H), 3.77 (dd, 2J = 8.6 Hz, 3J = 6.2 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.79 – 4.00 (m, 2H), 4.07 (dd, 2J = 8.5 Hz, 3J = 6.3 Hz, 1H), 4.87 (d, 2J = 6.2 Hz, 1H), 6.68 – 6.84 (m, 3H), 6.95 – 7.08 (m, 2H), 7.24 – 7.35 (m, 2H).

¹³C NMR (50 MHz, CDCl₃): δ 33.1, 42.4, 52.8, 56.00, 56.02, 60.7, 73.1, 82.4, 111.4, 112.0, 115.3 (d, 2J_C,F = 21.4 Hz), 120.5, 127.4 (d, 2J_C,F = 8.1 Hz), 133.0, 139.0 (d, 2J_C,F = 3.0 Hz), 147.5, 149.0, 162.2 (d, 2J_C,F = 245.1 Hz).

((2S,3R,4R)-4-(4-(tert-Butyl)benzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methanol (7d)
**Preparation:** analogous 7g, using crude starting material 8b (41.3 mg, 0.128 mmol, 1.0 equiv.) and 1-bromo-4-(tert-butyl)benzene (35.5 mg, 0.166 mmol, 1.3 equiv.) as aryl halide coupling partner.

**Work-up and purification:** the heterogeneous reaction content was filtered and rinsed with CH₂Cl₂ (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 80 : 20 in 60 min) afforded the title compound 7d.

Yield: 13.5 mg, 31 % (over 4 steps from unprotected alcohol 6b)

Appearance: nearly colorless oil

R<sub>f</sub> (silica): 0.49 (EtOAc / heptane, 1 : 1)

[α]<sup>D</sup>: +6.8 (c 1.07, MeOH)

LC-HRMS (ESI): calculated for M+H<sup>+</sup>: 343.2068, found: 343.2070, Δ: 0.62 ppm

(log<sub>P</sub><sup>calc</sup>): 5.44 ± 0.59

**1H NMR** (200 MHz, CDCl₃): δ 1.30 (s, 9H), 1.93 (bs, 1H), 2.32 (quint, <sup>3</sup>J = 6.4 Hz, 1H), 2.56 (dd, <sup>2</sup>J = 12.4 Hz, <sup>3</sup>J = 9.8 Hz, 1H), 2.63 – 2.82 (m, 1H), 2.88 (dd, <sup>2</sup>J = 12.5 Hz, <sup>3</sup>J = 4.7 Hz, 1H), 3.65 – 3.80 (m, 2H), 3.87 (dd, <sup>2</sup>J = 10.7 Hz, <sup>3</sup>J = 6.8 Hz, 1H), 4.06 (dd, <sup>2</sup>J = 8.5 Hz, <sup>3</sup>J = 6.4 Hz, 1H, H5), 4.88 (d, <sup>2</sup>J = 5.8 Hz, 1H, H2), 6.92 – 7.15 (m, 4H), 7.21 – 7.35 (m, 4H).

**13C NMR** (50 MHz, CDCl₃): δ 31.5, 32.9, 34.5, 42.1, 52.7, 60.8, 73.2, 82.5, 115.3 (d, <sup>2</sup>J<sub>C-F</sub> = 21.4 Hz), 125.6, 127.3 (d, <sup>1</sup>J<sub>C-F</sub> = 8.0 Hz), 128.3, 137.3, 139.1 (d, <sup>2</sup>J<sub>C-F</sub> = 3.1 Hz), 149.2, 162.2 (d, <sup>1</sup>J<sub>C-F</sub> = 245.1 Hz).

((2S,3R,4R)-2-(3,4-Dimethoxyphenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methanol (7e)

**Preparation:** a reaction vessel was charged with a stirring bar and crude starting material 8a (843.2 mg, 2.313 mmol), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 6.94 mL, 3.47 mmol) was added via syringe, the reaction was stirred for 35 h at 40 °C and then allowed to cool to room temperature. Water (42 µL, 2.3 mmol) was subsequently added and stirring was continued for 2 h to decompose excess 9-BBN. This mixture was then purged by bubbling argon into the solution through a needle, and dry and deoxygenated THF was added to produce a total volume of 13.0 mL, i.e. a 0.178 M solution of borylated intermediate, thus allowing the use of aliquots for subsequent coupling.
An aliquot (1.07 mL, 0.19 mmol, 1.0 equiv.) of this solution was transferred via syringe to a separate vessel which had been charged with a stirring bar, 1-bromo-4-(trifluoromethyl)benzene (55.6 mg, 0.247 mmol, 1.3 equiv.), Pd(dppf)Cl₂·CH₂Cl₂ (3.9 mg, 4.8 µmol, 2.5 mol %) and Cs₂CO₃ (310 mg, 0.950 mmol, 5.0 equiv.) under argon and was stirred for 50 h at room temperature. Following this, MgSO₄ (23 mg, 0.19 mmol, 1.0 equiv.) was added and stirring was continued for 1.5 h to remove residual water. For deprotection, a solution of TBAF (1.0 M in THF, 0.32 mL, 0.32 mmol, 1.7 equiv.) was added via syringe and the mixture was finally stirred for 24 h at room temperature.

Work-up and purification: the heterogeneous reaction content was filtered and rinsed with CH₂Cl₂ (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL/min, EtOAc / LP, 15 : 85 to 80 : 20 in 45 min) afforded the title compound 7e.

Yield: 57.2 mg, 76 % (over 4 steps from unprotected alcohol 6a)
Appearance: nearly colorless oil
Rₖ(silica): 0.59 (EtOAc)
[α]D²⁵: +18.7 (c 2.68, MeOH)
LC-HRMS (ESI): calculated for M+Na⁺: 419.1441, found: 419.1437, Δ: -0.95 ppm
(logP)calc: 4.01 ± 0.58

1H NMR (200 MHz, CDCl₃): δ 1.79 (bs, 1H), 2.42 (quint, ³J = 6.7 Hz, 1H), 2.60 – 2.86 (m, 2H), 3.04 (d, ²J = 11.4 Hz, 1H), 3.71 (dd, ²J = 8.6 Hz, ³J = 5.9 Hz, 1H), 3.76 – 3.97 (m, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.03 (dd, ²J = 8.6 Hz, ³J = 6.2 Hz, 1H), 4.82 (d, ³J = 6.4 Hz, 1H), 6.78 – 6.91 (m, 3H), 7.31 (d, ³J = 8.0 Hz, 2H), 7.55 (d, ²J = 8.2 Hz, 2H).

13C NMR (50 MHz, CDCl₃): δ 33.4, 42.1, 52.4, 55.99, 56.02, 60.8, 72.7, 82.8, 108.9, 111.1, 118.1, 124.3 (q, ²J_CF = 271.7 Hz), 125.6 (q, ³J_CF = 3.8 Hz), 128.7 (q, ²J_CF = 32.3 Hz), 129.1, 135.3, 144.8 (q, ²J_CF = 1.3 Hz), 148.5, 149.2.

Preparation: analogous to 7g, using crude starting material 8b (39.0 mg, 0.121 mmol, 1.0 equiv.) and 1-bromo-4-(trifluoromethyl)benzene (35.4 mg, 0.157 mmol, 1.3 equiv.) as aryl halide coupling partner.
Work-up and purification: the heterogeneous reaction content was filtered and rinsed with CH₂Cl₂ (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL/min, EtOAc / LP, 15 : 85 to 40 : 60 in 35 min) afforded the title compound 7f.

Yield: 17.5 mg, 41 % (over 4 steps from unprotected alcohol 6b)
Appearance: pale yellow oil
Rₖ(silica): 0.37 (EtOAc / heptane, 1 : 1)
[α]D²³: +12.0 (c 1.36, MeOH)
(logP)calc: 4.33 ± 0.62

((2S,3R,4R)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methanol (7f)
\[ {^1}H \text{ NMR (200 MHz, CDCl}_3\]: } \delta = 1.84 (bs, 1H), 2.36 (quint, \(J = 6.6 \text{ Hz, 1H}\)), 2.59 – 2.85 (m, 2H), 2.90 – 3.11 (m, 1H), 3.64 – 3.96 (m, 3H), 4.03 (dd, \(J = 8.5 \text{ Hz, } J = 6.2 \text{ Hz, 1H}\)), 4.87 (d, \(J = 6.1 \text{ Hz, 1H}\)), 7.01 (dd, \(J = 8.7 \text{ Hz, } J_{HF} = 8.7 \text{ Hz, 2H}\)), 7.20 – 7.35 (m, 4H), 7.54 (d, \(J = 8.2 \text{ Hz, 2H}\)).

\[ {^{13}}C \text{ NMR (50 MHz, CDCl}_3\]: } \delta = 33.4, 42.1, 52.6, 60.7, 72.8, 82.4, 115.4 (d, \(J_{CF} = 21.4 \text{ Hz}\)), 124.4 (q, \(J_{CF} = 271.9 \text{ Hz}\)), 125.6 (q, \(J_{CF} = 3.8 \text{ Hz}\)), 127.4 (d, \(J_{CF} = 3.1 \text{ Hz}\)), 128.8 (q, \(J_{CF} = 1.3 \text{ Hz}\)).

\((2S,3R,4R)-2\text{-Phenyl-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methanol (7g)}\)

**Preparation:** a reaction vessel was charged with a stirring bar and crude starting material 8c (44.5 mg, 0.118 mmol, 1.0 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 0.35 mL, 0.17 mmol, 1.5 equiv.) was added via syringe, the reaction was stirred for 24 h at 40 °C and then allowed to cool to room temperature. Water (2.5 µL, 0.13 mmol, 1.1 equiv.) was subsequently added and stirring was continued for 30 min to decompose excess 9-BBN, before the solution was transferred via syringe to a separate vessel which had been charged with a stirring bar, 1-bromo-4-(trifluoromethyl)benzene (34.6 mg, 0.154 mmol, 1.3 equiv.), Pd(dppf)Cl$_2$.CH$_2$Cl$_2$ (2.5 mol %), Cs$_2$CO$_3$ (5.0 equiv.) under argon and was stirred for 42 h at room temperature. Following this, MgSO$_4$ (14.4 mg, 0.12 mmol, 1.0 equiv.) was added and stirring was continued for 30 min to remove residual water. For deprotection, a solution of TBAF (1.0 M in THF, 0.18 mL, 0.17 mmol, 1.5 equiv.) was added via syringe and the mixture was finally stirred for 22 h at room temperature.

**Work-up and purification:** the heterogeneous reaction content was filtered and rinsed with CH$_2$Cl$_2$ (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 40 : 60 in 35 min) afforded the title compound 7g.

Yield: 17.4 mg, 44 % (over 4 steps from unprotected alcohol 6c)

Appearance: colorless oil

\[ [\alpha]_D^{23} = +15.3 \text{ (c 1.61, MeOH)} \]

\((2S,3R,4R)-4\text{-Fluorobenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methanol (7h)}\)

\[(2S,3R,4R)-4\text{-Fluorobenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methanol (7h)}\)
Preparation: analogous to 7c, using 1-bromo-4-fluorobenzene (35.4 mg, 0.202 mmol, 1.3 equiv.) as aryl halide coupling partner.

Work-up and purification: the heterogeneous reaction content was filtered and rinsed with CH$_2$Cl$_2$ (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL/min, EtOAc / LP, 10 : 90 to 60 : 40 in 35 min) afforded the title compound 7h.

Yield: 22.6 mg, 48 % (over 4 steps from unprotected alcohol 6b)

Appearance: light-brown oil

$R_t$ (silica): 0.41 (EtOAc / heptane, 1 : 1)

$[\alpha]_D^{23}$: +12.9 (c 0.77, MeOH)

$(\log P)_{calc}$: 3.81 ± 0.64

$^1$H NMR (200 MHz, CDCl$_3$): δ 1.47 (bs, 1H), 2.36 (quint, $^3$J = 6.5 Hz, 1H), 2.52 – 2.82 (m, 2H), 2.94 (dd, $^2$J = 12.3 Hz, $^3$J = 3.9 Hz, 1H), 3.67 – 3.98 (m, 3H), 4.05 (dd, $^2$J = 8.6 Hz, $^3$J = 6.3 Hz, 1H), 4.88 (d, $^3$J = 6.0 Hz, 1H), 6.92 – 7.19 (m, 2H), 7.23 – 7.34 (m, 2H).

$^{13}$C NMR (50 MHz, CDCl$_3$): δ 32.7, 42.6, 52.7, 60.7, 72.8, 82.7, 115.5 (d, $^2$J$_{C,F}$ = 21.4 Hz), 115.6 (d, $^2$J$_{C,F}$ = 21.3 Hz), 127.5 (d, $^3$J$_{C,F}$ = 8.2 Hz), 130.2 (d, $^3$J$_{C,F}$ = 7.7 Hz), 135.7 (d, $^4$J$_{C,F}$ = 3.3 Hz), 138.5 (d, $^4$J$_{C,F}$ = 3.2 Hz), 161.7 (d, $^1$J$_{C,F}$ = 244.5 Hz), 162.3 (d, $^1$J$_{C,F}$ = 245.8 Hz).

General Outline for Mitsunobu Esterification

All compounds of generic structure 1 in this section were prepared according to the General Outline above, and are arranged such that compounds with the same $R^1$ are grouped together. Thus, for the Preparation of any particular compound, the experimental details are either given in full, or the reader is referred to an analogous procedure already described for a compound in this section. Generally, reaction progress was monitored by TLC or GC-MS, and the reaction was terminated when complete. Details for Work-up and purification are given for each case individually to afford compounds of structure 1a-l.

(Z)-(2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (leoligin, 1a)
**Preparation:** a reaction vessel was charged with a stirring bar, starting material 7a (989 mg, 2.55 mmol, 1.0 equiv.), angelic acid (383 mg, 3.83 mmol, 1.5 equiv.) and PPh$_3$ (2.34 g, 8.93 mmol, 3.5 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (20 mL) was then added and the solution cooled to 0 °C in an ice bath. To the stirred mixture was then added DEAD (1.40 mL, 8.93 mmol, 3.5 equiv.) dropwise via syringe, and the reaction stirred for 12 h while being kept away from light and allowed to warm slowly to room temperature.

**Work-up and purification:** The solvent was evaporated, which was followed by the addition of CHCl$_3$ (15 mL), LP (300 mL) and water (200 mL). The layers were separated and the aqueous phase was re-extracted with LP (4 x 50 ml). The solvents were evaporated from the combined organic phases and then flash column chromatography was performed (180 g silica, flow rate 40 mL / min, EtOAc / LP, 25 : 75 to 50 : 50 in 60 min) to afford the title compound 1a. An analytical sample could be crystallized from a saturated solution of heptane and cooling it to -20 °C for several days. Leoligin is a literature-known natural compound.

**Yield:** 1.124 g, 94 %

**Appearance:** nearly colorless oil

**Melting range:** 45.0 – 46.5 °C; lit.\textsuperscript{13} melting range: n/a (natural compound obtained as a colorless amorphous substance)

**R$_f$ (silica):** 0.57 (EtOAc / LP, 1 : 1)

**$[\alpha]_D^{25}$**:

- +23.4 (c 3.69, MeOH); lit.\textsuperscript{13} $[\alpha]_D^{25}$: +25 (c 0.002, CH$_2$Cl$_2$)

**LC-HRMS (ESI):** calculated for M+Na$^+$: 493.2197, found: 493.2201, $\Delta$: 0.81 ppm

**GC-MS (EI, 70 eV, Method E):** 23.65 min; 470.2 (M$^+$, 3), 219.1 (26), 189.1 (15), 177.1 (15), 165.1 (72), 151.0 (100), 107.1 (15).\textsuperscript{13}

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.85 – 1.90 (m, 3H, H5'''), 2.00 (dq, $^3J$ = 7.2 Hz, $^5J$ = 1.5 Hz, 3H, H4'''), 2.49 – 2.85 (m, 3H, H3, H4, C4-C), 2.90 (dd, $^1J$ = 12.4 Hz, $^3J$ = 4.2 Hz, 1H, C4-CH), 3.78 (dd, $^1J$ = 8.6 Hz, $^3J$ = 6.0 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH$_3$), 3.87 (s, 6H, Ar-OCH$_3$), 3.88 (s, 3H, Ar-OCH$_3$), 4.08 (dd, $^1J$ = 8.6 Hz, $^3J$ = 6.2 Hz, 1H, H5), 4.28 (dd, $^1J$ = 11.3 Hz, $^3J$ = 7.0 Hz, 1H, C3-CH), 4.42 (dd, $^1J$ = 11.3 Hz, $^3J$ = 7.0 Hz, 1H, C3-CH), 4.84 (d, $^3J$ = 6.3 Hz, 1H, H2), 6.10 (qq, $^3J$ = 7.2 Hz, $^4J$ = 1.3 Hz, 1H, H3'''), 6.67 – 6.75 (m, 2H, H2'', H6''), 6.77 – 6.90 (m, 4H, H2, H5', H6', H5'').\textsuperscript{13}

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.3 (t, C4-C), 42.8 (d, C4), 49.3 (d, C3), 56.0 (q, 2 x Ar-OCH$_3$), 56.0 (q, Ar-OCH$_3$), 56.1 (q, Ar-OCH$_3$), 62.3 (t, C3-C), 72.8 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 111.4 (d, C5'''), 112.0 (d, C2'''), 118.2 (d, C6'), 120.6 (d, C6'), 127.5 (s, C2'''), 132.7 (s, C1''), 135.1 (s, C1'), 139.0 (d, C3'''), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 167.8 (s, C1'').
Preparation: a reaction vessel was charged with a stirring bar, starting material 7b (31.1 mg, 0.081 mmol, 1.00 equiv.), angelic acid (12.2 mg, 0.122 mmol, 1.5 equiv.) and PPh₃ (74.4 mg, 0.284 mmol, 3.5 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (0.75 mL) was then added via syringe and the solution cooled to 0 °C in an ice bath. To the stirred mixture was then added a solution of ADD (71.5 mg, 0.284 mmol, 3.5 equiv.) in dry THF (1.5 mL) via syringe over approximately 1 min, and the reaction stirred for 22 h while being kept away from light and allowed to warm slowly to room temperature.

Work-up and purification: Et₂O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et₂O (15 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 7 : 93 isocratically for 3 min, then to 35 : 65 in 30 min) afforded the title compound 1f.

Yield: 25.4 mg, 67 %
Appearance: colorless oil
Rᵣ (silica): 0.78 (EtOAc / LP, 1 : 1)
[α]₂₀: +21.4 (c 1.52, MeOH)
LC-HRMS (APCI): calculated for M+Na⁺: 489.2611, found: 489.2676, Δ: 13.29 ppm
(log P)calc: 7.33 ± 0.46
Preparation: analogous to 1a, using starting material 7c (36.4 mg, 0.105 mmol, 1.0 equiv.) and stirring for 18 in place of 12 h.

Work-up and purification: The solvent was evaporated, which was followed by the addition of CHCl₃ (1.0 mL), LP (10 mL) and water (10 mL). The layers were separated and the aqueous phase was re-extracted with LP. The solvents were evaporated from the combined organic phases and flash column chromatography was performed (45 g silica, flow rate 30 mL / min, EtOAc / LP, 3 : 97 isocratically for 3 min, then to 50 : 50 in 40 min), followed by preparative HPLC (flow rate 20.0 mL / min, MeOH / water, 73 : 27 isocratically for 25 min, then to 77 : 23 in 15 min), to afford the title compound 1g.

Yield: 24.7 mg, 55 %
Appearance: colorless oil
R<sub>f</sub> (silica): 0.47 (EtOAc / LP, 1 : 2)
[α]<sub>D</sub><sup>23</sup>: +15.9 (c 0.90, MeOH)
LC-HRMS (ESI): calculated for M+Na<sup>+</sup>: 451.1891, found: 451.1892, ∆: 0.22 ppm

(1H NMR (200 MHz, CDCl₃): δ 1.83 – 1.89 (m, 3H), 2.00 (dq, <sup>3</sup>J = 7.2 Hz, <sup>5</sup>J = 1.5 Hz, 3H), 2.49 – 2.84 (m, 3H), 2.89 (dd, <sup>2</sup>J = 12.5 Hz, <sup>3</sup>J = 4.2 Hz, 1H), 3.79 (dd, <sup>2</sup>J = 8.6 Hz, <sup>3</sup>J = 6.2 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 4.08 (dd, <sup>2</sup>J = 8.6 Hz, <sup>3</sup>J = 6.2 Hz, 1H), 4.27 (dd, <sup>2</sup>J = 11.3 Hz, <sup>3</sup>J = 7.3 Hz, 1H), 4.43 (dd, <sup>2</sup>J = 11.3 Hz, <sup>3</sup>J = 6.8 Hz, 1H), 4.89 (d, <sup>3</sup>J = 6.1 Hz, 1H), 6.10 (qq, <sup>3</sup>J = 7.2 Hz, <sup>4</sup>J = 1.4 Hz, 1H), 6.65 – 6.84 (m, 3H), 6.95 – 7.08 (m, 2H), 7.23 – 7.34 (m, 2H).

(13C NMR (50 MHz, CDCl₃): δ 16.0, 20.7, 33.2, 42.8, 49.5, 56.00, 56.02, 62.2, 72.9, 82.7, 111.5, 112.0, 115.4 (d, <sup>2</sup>J<sub>CF</sub> = 21.4 Hz), 120.6, 127.5 (d, <sup>2</sup>J<sub>CF</sub> = 8.1 Hz), 132.6, 138.5 (d, <sup>2</sup>J<sub>CF</sub> = 3.0 Hz), 139.2, 147.7, 149.1, 162.4 (d, <sup>1</sup>J<sub>CF</sub> = 245.6 Hz), 167.8; One carbon signal not visible due to signal overlap.

GC-MS (El, 70 eV, Method E): 13.03 min; 428.2 (M<sup>+</sup>, 4), 194.1 (21), 190.1 (18), 189.1 (19), 177.1 (38), 164.1 (23), 163.1 (15), 152.1 (29), 151.0 (100), 123.0 (55), 109.0 (37), 107.1 (22).

log (<sup>P</sup>)<sub>calc</sub>: 5.69 ± 0.52
(Z)-((2S,3R,4R)-4-(4-(tert-Butyl)benzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (1h)

**Preparation:** analogous to 1k, using starting material 7d (10.5 mg, 0.031 mmol, 1.0 equiv.). First leg: angelic acid (4.6 mg, 0.046 mmol, 1.5 equiv.), ADD (27.1 mg, 0.108 mmol, 3.5 equiv.), PPh₃ (28.2 mg, 0.108 mmol, 3.5 equiv.), stirring for 18.5 h. Second leg: angelic acid (4.6 mg, 0.046 mmol, 1.5 equiv.), ADD (27.1 mg, 0.108 mmol, 3.5 equiv.), PPh₃ (28.2 mg, 0.108 mmol, 3.5 equiv.), stirring for 47 h.

**Work-up and purification:** the solvent was evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 2 : 98 to 10 : 90 in 40 min) afforded the title compound 1h.

**Yield:** 4.9 mg, 37%

**Appearance:** colorless oil

**Rₖ (silica):** 0.83 (EtOAc / heptane, 1 : 1)

**[α]D²₀:** +9.2 (c 0.69, i-PrOH)

**LC-HRMS (APCI):** calculated for M+H⁺: 425.2486, found: 425.2503, Δ: 4.00 ppm

**(log P)calc:** 7.64 ± 0.50

**GC-MS (EI, 70 eV, Method E):** 10.35 min; 185.1 (42), 177.0 (68), 175.1 (36), 147.1 (p-tert-butylbenzyl, 30), 145.1 (30), 132.1 (42), 131.1 (29), 129.1 (46), 123.0 (100), 117.0 (57), 109.0 (33). M⁺ not visible.

**¹H NMR (200 MHz, CDCl₃):** δ 1.31 (s, 9H), 1.83 – 1.90 (m, 3H), 1.99 (dq, 3J = 7.2 Hz, 5J = 1.5 Hz, 3H), 2.49 – 2.85 (m, 3H), 2.90 (dd, 3J = 12.5 Hz, 1J = 4.2 Hz, 1H), 3.78 (dd, 3J = 8.6 Hz, 1J = 6.4 Hz, 1H), 4.09 (dd, 3J = 8.6 Hz, 1J = 6.3 Hz, 1H), 4.28 (dd, 3J = 11.3 Hz, 1J = 7.3 Hz, 1H), 4.42 (dd, 3J = 11.3 Hz, 1J = 6.7 Hz, 1H), 4.89 (d, 3J = 5.9 Hz, 1H), 5.98 – 6.21 (m, 1H), 6.95 – 7.15 (m, 4H), 7.22 – 7.37 (m, 4H).

**¹³C NMR (50 MHz, CDCl₃):** δ 16.0, 20.7, 31.5, 33.1, 34.5, 42.5, 49.6, 62.3, 73.0, 82.7, 115.4 (d, 3JCF = 21.5 Hz), 125.7, 127.5, 127.5 (d, 3JCF = 8.1 Hz), 128.4, 137.0, 138.6 (d, 4JCF = 3.1 Hz), 139.2, 149.3, 162.4 (d, 4JCF = 245.5 Hz), 167.9.

(Z)-((2S,3R,4R)-2-(3,4-Dimethoxyphenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (1i)

**Preparation:** analogous to 1f, using starting material 7e (32.7 mg, 0.082 mmol, 1.00 equiv.).

**Metallosynthesis:** angelic acid (1.5 equiv.), ADD (3.5 equiv.), PPh₃ (3.5 equiv.).
Work-up and purification: Et₂O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et₂O (15 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 40 : 60 in 40 min) afforded the title compound 1i.

Yield: 34.3 mg, 87 %
Appearance: colorless oil
R₉ (silica): 0.74 (EtOAc / cyclohexane, 1 : 1)
[α]D₂₀: +28.5 (c 0.97, MeOH)
(log P)calc: 6.21 ± 0.49

GC-MS (EI, 70 eV, Method E): 12.47 min; 478.1 (M⁺, 2), 219.0 (28), 166.1 (39), 165.0 (100), 159.0 (25). ¹H NMR (200 MHz, CDCl₃): δ 1.85 – 1.90 (m, 3H), 2.00 (dq, 3J = 7.2 Hz, 5J = 1.5 Hz, 3H), 2.55 – 2.89 (m, 3H, H₃, H₄), 2.95 – 3.07 (m, 1H), 3.74 (dd, 2J = 8.7 Hz, 3J = 5.9 Hz, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 4.07 (dd, 2J = 8.8 Hz, 3J = 6.0 Hz, 1H), 4.28 (dd, 2J = 11.4 Hz, 3J = 6.6 Hz, 1H), 4.40 (dd, 2J = 11.4 Hz, 3J = 7.1 Hz, 1H), 4.84 (d, 3J = 6.4 Hz, 1H, H₂), 6.12 (qq, 3J = 7.2 Hz, 4J = 1.3 Hz, 1H), 6.79 – 6.92 (m, 3H), 7.30 (d, 3J = 8.1 Hz, 2H), 7.56 (d, 3J = 8.1 Hz, 2H).

¹³C NMR (50 MHz, CDCl₃): δ 16.0, 20.7, 33.6, 42.3, 49.3, 56.0, 56.1, 62.1, 72.6, 82.9, 108.9, 111.2, 118.2, 124.3 (q, 3J_C-F = 272.0 Hz), 125.7 (q, 3J_C-F = 3.8 Hz), 127.4, 128.9 (q, 3J_C-F = 32.3 Hz), 129.1, 134.8, 139.3, 144.4 (q, 3J_C-F = 1.3 Hz), 148.7, 149.2, 167.8.

GC-MS (EI, 70 eV, Method E): 8.11 min; 437.1734, found: 437.1756, Δ: 5.03 ppm
(log P)calc: 6.53 ± 0.54

Preparation: analogous to 1f, using starting material 7f (13.3 mg, 0.038 mmol, 1.0 equiv.) and stirring for 18.5 in place of 22 h.
Work-up and purification: the solvent was evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 2 : 98 to 10 : 90 in 30 min) afforded the title compound 1j.

Yield: 10.1 mg, 61 %
Appearance: colorless oil
R₉ (silica): 0.79 (EtOAc / heptane, 1 : 1)
[α]D₂₀: +13.8 (c 1.02, i-PrOH)
LC-HRMS (ESI): calculated for M+H⁺: 437.1734, found: 437.1756, Δ: 5.03 ppm
(log P)calc: 6.53 ± 0.54

GC-MS (EI, 70 eV, Method E): 8.11 min; 336.0 (20), 212.0 (16), 185.0 (16), 177.0 (78), 164.1 (20), 159.0 (p-trifluoromethylbenzyl, 73), 125.0 (39), 123.0 (100), 109.0 (35). M⁺ not visible. ¹H NMR (200 MHz, CDCl₃): δ 1.83 – 1.90 (m, 3H), 2.00 (dq, 3J = 7.2 Hz, 5J = 1.5 Hz, 3H), 2.50 – 2.96 (m, 3H), 2.93 – 3.06 (m, 1H), 3.75 (dd, 2J = 8.7 Hz, 5J = 6.0 Hz, 1H), 4.07 (dd, 2J = 11.4 Hz, 3J = 6.0 Hz, 1H), 4.28 (dd, 2J = 11.4 Hz, 3J = 7.1 Hz, 1H).
(dd, \(J = 11.4\) Hz, \(J = 6.9\) Hz, 1H), 4.41 (dd, \(J = 11.4\) Hz, \(J = 6.9\) Hz, 1H), 4.89 (d, \(J = 6.2\) Hz, 1H), 6.12 (qq, \(J = 7.2\) Hz, \(J = 1.4\) Hz, 1H), 6.95 – 7.11 (m, 2H), 7.22 – 7.36 (m, 4H), 7.56 (d, \(J = 8.2\) Hz, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 15.8, 20.6, 33.4, 42.2, 49.4, 61.9, 72.5, 82.5, 115.4\) (dd, \(J_{C-F} = 21.5\) Hz), 124.2 (q, \(J_{C-F} = 271.9\) Hz), 125.6 (q, \(J_{C-F} = 3.7\) Hz), 127.2, 127.3 (d, \(J_{C-F} = 8.1\) Hz), 128.8 (q, \(J_{C-F} = 32.5\) Hz), 128.9, 138.0 (d, \(J_{C-F} = 3.1\) Hz), 139.3, 144.1 (q, \(J_{C-F} = 1.1\) Hz), 162.3 (d, \(J_{C-F} = 245.8\) Hz), 167.6.

\((Z)-((2S,3R,4R)-2-Phenyl-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (1k)

**Preparation:** a reaction vessel was charged with a stirring bar, starting material 7g (15.3 mg, 0.045 mmol, 1.0 equiv.), angelic acid (6.8 mg, 0.068 mmol, 1.5 equiv.) and PPh\(_3\) (41.7 mg, 0.159 mmol, 3.5 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (0.75 mL) was then added and the solution cooled to 0 °C in an ice bath. To the stirred mixture was then added a solution of ADD (40.1 mg, 0.159 mmol, 3.5 equiv.) in dry THF (1.0 mL) via syringe over approximately 1 min, and the reaction stirred for 16 h while being kept away from light and allowed to warm slowly to room temperature (first leg). Then the reaction was cooled in an ice bath again, and there was added more angelic acid (6.8 mg, 0.068 mmol, 1.5 equiv.) and PPh\(_3\) (41.7 mg, 0.159 mmol, 3.5 equiv.) in dry THF (0.75 mL) via syringe, followed by the addition of more ADD (40.1 mg, 0.159 mmol, 3.5 equiv.) in dry THF (1.0 mL) via syringe over approximately 1 min, and the reaction stirred for 16 h while being kept away from light and allowed to warm slowly to room temperature again (second leg).

**Work-up and purification:** the solvent was evaporated and flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 2 : 98 to 10 : 90 in 30 min) afforded the title compound 1k.

**Appearance:** colorless oil

**\(R_f\) (silica):** 0.80 (EtOAc / heptane, 1 : 1)

**\([\alpha]_{D}^{20}\):** +16.3 (c 0.74, i-PrOH)

**LC-HRMS (APCI):** calculated for M+H\(^+\): 419.1829, found: 419.1840, \(\Delta\): 2.62 ppm

**GC-MS (EI, 70 eV, Method E):** 8.19 min; 159.0 (p-trifluoromethylbenzyl, 100), 146.1 (15), 115.0 (15), 107.0 (34), 105.0 (77), 91.1 (21). M\(^+\) not visible.

\(^{1}H\) NMR (200 MHz, CDCl\(_3\)): \(\delta = 1.85 – 1.91\) (m, 3H), 2.00 (dq, \(J = 7.2\) Hz, \(J = 1.5\) Hz, 3H), 2.56 – 2.91 (m, 3H), 2.94 – 3.05 (m, 1H), 3.77 (dd, \(J = 8.7\) Hz, \(J = 6.1\) Hz, 1H), 4.09 (dd, \(J = 8.7\) Hz, \(J = 6.0\) Hz, 1H), 4.29 (dd, \(J = 11.3\) Hz, \(J = 6.8\) Hz, 1H), 4.42 (dd, \(J = 11.4\) Hz, \(J = 7.0\) Hz, 1H), 4.93 (d, \(J = 5.9\) Hz, 1H), 6.11 (qq, \(J = 7.2\) Hz, \(J = 1.3\) Hz, 1H), 7.22 – 7.40 (m, 7H), 7.55 (d, \(J = 8.2\) Hz, 2H).
$^{13}$C NMR (50 MHz, CDCl$_3$): δ 16.0, 20.7, 33.6, 42.3, 49.6, 62.1, 72.7, 83.1, 124.3 (q, $^1J_{CF}$ = 271.9 Hz), 125.7 (q, $^3J_{CF}$ = 3.8 Hz), 125.8, 127.4, 127.8, 128.9 (q, $^3J_{CF}$ = 32.5 Hz), 128.7, 129.1, 139.3, 142.6, 144.4 (q, $^5J_{CF}$ = 1.2 Hz), 167.8.

(Z)-(2S,3R,4R)-4-(4-Fluorobenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (1l)

Preparation: analogous to 1k, using starting material 7h (20.9 mg, 0.069 mmol, 1.0 equiv.). First leg: angelic acid (10.3 mg, 0.103 mmol, 1.5 equiv.), ADD (60.7 mg, 0.241 mmol, 3.5 equiv.), PPh$_3$ (63.1 mg, 0.241 mmol, 3.5 equiv.), stirring for 16 h. Second leg: angelic acid (10.3 mg, 0.103 mmol, 1.5 equiv.), ADD (60.7 mg, 0.241 mmol, 3.5 equiv.), PPh$_3$ (63.1 mg, 0.241 mmol, 3.5 equiv.), stirring for 21 h.

Work-up and purification: the solvent was evaporated and flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 0 : 100 to 10 : 90 in 50 min) afforded the title compound 1l.

Yield: 17.1 mg, 64 %
Appearance: colorless oil
$R_f$(silica): 0.75 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{25}$: +15.2 (c 1.13, i-PrOH)
LC-HRMS (APCI): calculated for M+Na$: 421.1786$, found: 421.1791, $\Delta$: 1.19 ppm

$^{1}H$ NMR (200 MHz, CDCl$_3$): δ 1.83 – 1.90 (m, 3H), 1.99 (dq, $^3J$ = 7.3 Hz, $^5J$ = 1.5 Hz, 3H), 2.49 – 2.83 (m, 3H), 2.91 (dd, $^2J$ = 12.2 Hz, $^3J$ = 3.7 Hz, 1H), 3.75 (dd, $^2J$ = 8.7 Hz, $^3J$ = 6.2 Hz, 1H), 4.06 (dd, $^2J$ = 8.7 Hz, $^3J$ = 6.1 Hz, 1H), 4.26 (dd, $^2J$ = 11.4 Hz, $^3J$ = 7.1 Hz, 1H), 4.40 (dd, $^2J$ = 11.4 Hz, $^3J$ = 6.8 Hz, 1H), 4.88 (d, $^3J$ = 6.1 Hz, 1H), 6.11 (qq, $^3J$ = 7.3 Hz, $^4J$ = 1.4 Hz, 1H), 6.92 – 7.18 (m, 6H), 7.23 – 7.34 (m, 2H).

$^{13}$C NMR (50 MHz, CDCl$_3$): δ 16.0, 20.7, 32.9, 42.7, 49.5, 62.1, 72.8, 82.7, 115.5 (d, $^2J_{CF}$ = 21.5 Hz), 115.6 (d, $^3J_{CF}$ = 21.3 Hz), 127.4, 127.5 (d, $^3J_{CF}$ = 8.3 Hz), 130.1 (d, $^3J_{CF}$ = 7.8 Hz), 135.7 (d, $^4J_{CF}$ = 3.3 Hz), 138.4 (d, $^4J_{CF}$ = 3.1 Hz), 139.3, 161.7 (d, $^1J_{CF}$ = 244.4 Hz), 162.4 (d, $^1J_{CF}$ = 245.8 Hz), 167.8.

1l, C$_{23}$H$_{24}$F$_2$O$_3$ 386.43 g mol$^{-1}$
General Outline for Steglich Esterification

All compounds of generic structure 1 in this section were prepared according to the General Outline above, and are arranged such that compounds with the same $R^3$ are grouped together. Thus, for the Preparation of any particular compound, the experimental details are either given in full, or the reader is referred to an analogous procedure already described for a compound in this section. Generally, reaction progress was monitored by TLC or GC-MS, and the reaction was terminated when complete. Details for Work-up and purification are given for each case individually to afford compounds of structure 1b–e.

$$((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 3-methylbut-2-enoate (1b)$$

Preparation: a reaction vessel was charged with a stirring bar, 3-methylbut-2-enoic acid (36.0 mg, 0.360 mmol, 4.0 equiv.) and 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique (1 x). Dry CH$_2$Cl$_2$ (1.0 mL) was then added via syringe and the solution was cooled to 0 °C in an ice bath. The vessel was briefly opened, EDCI.HCl (63.8 mg, 0.333 mmol, 3.7 equiv.) added in one go and the mixture was stirred for 3 h at 0 °C. Meanwhile, a second vessel was charged with a stirring bar and starting material 7a (35.0 mg, 0.090 mmol, 1.00 equiv.), evacuated and back-filled with argon (3 x), and DIPEA (78 µL, 0.45 mmol, 5.0 equiv.) was added via syringe. After 3 h, the solution containing the activated carboxylic acid was transferred to the second vial via syringe and stirred for 16 h at room temperature. The reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to give a mixture of the targeted compound 1b, as well as $\beta$-$\gamma$ double bond isomerization compound 1b’ (approximate ratio 3 : 1, by NMR, 34.4 mg). Thus, a new reaction vessel was charged with a stirring bar and part of the so obtained material (24.7 mg, 0.052 mmol), evacuated and back-filled with argon. To this was then added tert-BuOK (2.9 mg, 0.026 mmol) in dry THF (1.0 mL) via syringe and the solution stirred at room temperature for 18 h.

Work-up and purification: THF (1.0 mL) was added, followed by Et$_2$O (15 mL) and a solution of KHSO$_4$ (0.029 mmol, 3.9 mg) in brine (2 mL). Water (1.5 mL) was added to dissolve the salts, the layers were separated, the aqueous phase was re-extracted with Et$_2$O (2 x 10 mL), the combined organic phases
were dried with Na$_2$SO$_4$, filtered and the solvents were evaporated. Finally, flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 50 : 50 in 30 min) afforded the title compound 1b.

**Yield:** 17.0 mg, 40 % (with respect to the amount of starting material 7a), 56 % (with respect also to the amount of α-β- and β-γ- mixture applied for de-isomerization), respectively

**Appearance:** nearly colorless oil

**R$_f$ (silica):** 0.50 (EtOAc / heptane, 1 : 1)

**$[\alpha]_D^{20}$:** +29.2 (c 1.63, MeOH)

**LC-HRMS (ESI):** calculated for M+Na$^+$: 493.2197, found: 493.2201, Δ: 0.81 ppm

**($\log P$)$_{calc}$:** 5.38 ± 0.48

**GC-MS (EI, 70 eV, Method E):** 25.73 min; 470.2 (M$^+$, 2), 219.1 (29), 189.1 (17), 177.1 (16), 166.1 (15), 165.0 (89), 152.1 (15), 151.1 (100), 107.0 (18).

**$^1$H NMR (200 MHz, CDCl$_3$):** δ 1.90 (d, $^4_J = 1.1$ Hz, 3H), 2.17 (d, $^4_J = 1.1$ Hz, 3H), 2.47 – 2.84 (m, 3H), 2.89 (dd, $^2_J = 12.6$ Hz, $^3_J = 4.3$ Hz, 1H), 3.75 (dd, $^2_J = 8.6$ Hz, $^3_J = 6.4$ Hz, 1H), 3.86 (s, 3H), 3.87 (s, 6H), 3.88 (s, 3H), 4.07 (d, $^2_J = 8.5$ Hz, $^3_J = 6.2$ Hz, 1H), 4.21 (dd, $^2_J = 11.3$ Hz, $^3_J = 6.9$ Hz, 1H), 4.37 (dd, $^2_J = 11.3$ Hz, $^3_J = 7.1$ Hz, 1H), 4.81 (d, $^3_J = 6.3$ Hz, 1H), 5.62 – 5.68 (m, 1H), 6.67 – 6.91 (m, 6H).

**$^{13}$C NMR (50 MHz, CDCl$_3$):** δ 20.4, 27.6, 33.3, 42.7, 49.3, 55.9, 55.9, 56.0, 56.1, 61.8, 72.9, 83.1, 109.0, 111.1, 111.5, 112.1, 115.7, 118.2, 120.6, 132.9, 135.2, 147.6, 148.5, 149.1, 149.1, 157.7, 166.6.

((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 3-methylbutanoate (1c)

**Preparation:** a reaction vessel was charged with a stirring bar, 3-methylbutanoic acid (13.8 mg, 0.135 mmol, 2.3 equiv.) and 4-DMAP (0.7 mg, 5.9 µmol, 0.1 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry CH$_2$Cl$_2$ (1.0 mL) was then added via syringe and the solution was cooled to 0 °C in an ice bath. The vessel was briefly opened, EDCI.HCl (22.5 mg, 0.117 mmol, 2.0 equiv.) added in one go and the mixture was stirred for 3 h at 0 °C. Meanwhile, a second vessel was charged with a stirring bar and starting material 7a (22.8 mg, 0.059 mmol, 1.00 equiv.), evacuated and back-filled with argon (3 x), and DIPEA (26 µL, 0.15 mmol, 2.5 equiv.) was added via syringe. After 3 h, the solution containing the activated carboxylic acid was transferred to the second vial via syringe and stirred for 16 h at room temperature.

**Work-up and purification:** the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 30 : 70 in 30 min) to afford the title compound 1c.

**Yield:** 22.0 mg, 96 %

**Appearance:** colorless oil

**R$_f$ (silica):** 0.45 (EtOAc / heptane, 1 : 1)
([α]_D)\text{^23} = +22.9 (c 0.90, MeOH)

LC-HRMS (APCI): calculated for M+Na\(^+\): 495.2353, found: 495.2371, Δ: 3.63 ppm

(\log P)_{\text{calc}} = 5.10 ± 0.45

GC-MS (EI, 70 eV, Method F): 21.28 min; 472.1 (M\(^+\), 9), 219.1 (25), 189.1 (15), 165.0 (55), 152.1 (15), 151.0 (100).

\(^1\)H NMR (200 MHz, CDCl\(_3\)): δ 0.96 (d, \(J = 6.4\) Hz, 6H), 1.97 – 2.22 (m, 3H), 2.47 – 2.64 (m, 2H), 2.64 – 2.81 (m, 1H), 2.87 (dd, \(J = 12.5\) Hz, \(J = 6.4\) Hz, 1H), 3.75 (dd, \(J = 8.6\) Hz, \(J = 6.2\) Hz, 1H), 3.86 (s, 3H), 3.87 (s, 6H), 3.89 (s, 3H), 4.07 (dd, \(J = 8.6\) Hz, \(J = 6.3\) Hz, 1H), 4.18 (dd, \(J = 11.3\) Hz, \(J = 7.1\) Hz, 1H), 4.38 (dd, \(J = 11.2\) Hz, \(J = 7.0\) Hz, 1H), 4.79 (d, \(J = 6.4\) Hz, 1H), 6.66 – 6.90 (m, 6H).

\(^{13}\)C NMR (50 MHz, CDCl\(_3\)): δ 22.6, 25.8, 33.3, 42.6, 43.5, 49.2, 56.0, 62.5, 72.8, 83.0, 109.0, 111.1, 111.5, 112.0, 118.2, 120.6, 132.7, 135.1, 147.6, 148.6, 149.1, 149.2, 173.1.

\((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl pivalate (1d)

Preparation: a reaction vessel was charged with a stirring bar, pivalic acid (21.1 mg, 0.207 mmol, 2.3 equiv.) and 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry CH\(_2\)Cl\(_2\) (1.0 mL) was then added via syringe and the solution was cooled to 0 °C in an ice bath. The vessel was briefly opened, EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.) added in one go and the mixture was stirred for 3 h at 0 °C. Meanwhile, a second vessel was charged with a stirring bar and 7a (35.0 mg, 0.090 mmol, 1.00 equiv.), evacuated and back-filled with argon (3 x), and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.) was added via syringe. After 3 h, the solution containing the activated carboxylic acid was transferred to the second vial via syringe and stirred for 70 h at room temperature. To complete the reaction, more of the activated carboxylic acid was prepared in a separate vessel in the same way as above (using pivalic acid (18.3 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and EDCI.HCl (30.0 mg, 0.157 mmol, 1.7 equiv.)) and then, after 3 h at 0 °C, added to the reaction vial, followed by more DIPEA (39 µL, 0.23 mmol, 2.5 equiv.) via syringe, and the mixture was stirred for another 96 h at room temperature.

Work-up and purification: the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 38 : 62 in 12 min, then to 100 : 0 in 10 min) to afford the title compound 1d.

Yield: 32.2 mg, 76 %

Appearance: colorless oil

R\(_f\) (silica): 0.49 (EtOAc / LP, 1 : 1)

([α]_D)\text{^23} = +22.5 (c 2.72, MeOH)

LC-HRMS (ESI): calculated for M+Na\(^+\): 495.2353, found: 495.2351, Δ: -0.40 ppm

(\log P)_{\text{calc}} = 4.91 ± 0.45
GC-MS (EI, 70 eV, Method E): 19.53 min; 472.2 (M^+, 5), 219.1 (25), 165.1 (54), 152.1 (15), 151.1 (100).

^1H NMR (200 MHz, CDCl3): δ 1.21 (s, 9H), 2.45 – 2.81 (m, 3H), 2.87 (dd, 2J = 12.4 Hz, 3J = 4.1 Hz, 1H), 3.77 (dd, 2J = 8.6 Hz, 3J = 6.2 Hz, 1H), 3.88 (s, 9H), 3.89 (s, 3H), 4.07 (dd, 2J = 8.6 Hz, 3J = 6.3 Hz, 1H), 4.17 (dd, 2J = 11.3 Hz, 3J = 6.8 Hz, 1H), 4.36 (dd, 2J = 11.3 Hz, 3J = 6.9 Hz, 1H), 4.82 (d, 2J = 6.3 Hz, 1H), 6.66 – 6.90 (m, 6H).

^13C NMR (50 MHz, CDCl3): δ 27.3, 33.3, 38.9, 42.8, 49.4, 55.98, 56.00, 56.03, 56.1, 62.7, 72.8, 82.9, 109.0, 111.2, 111.4, 112.0, 118.1, 120.6, 132.7, 135.1, 147.6, 148.6, 149.1, 149.2, 178.5.

((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl cycloheptanecarboxylate (1e)

Preparation: analogous to 1c, using starting material 7a (35.0 mg, 0.090 mmol, 1.00 equiv.), cycloheptanecarboxylic acid (29.4 mg, 0.207 mmol, 2.3 equiv.), EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.).

Work-up and purification: the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 15 : 85 in 10 min, then to 25 : 75 in 7 min, then to 50 : 50 in 12 min) to afford the title compound 1e.

Yield: 38.8 mg, 84 %

Appearance: colorless oil

Rf (silica): 0.53 (EtOAc / LP, 1 : 1)

[α]D^25: +20.0 (c 3.74, MeOH)

LC-HRMS (ESI): calculated for M+H+: 513.2847, found: 513.2842, Δ: -0.87 ppm

(log P)calc: 6.31 ± 0.44

^1H NMR (200 MHz, CDCl3): δ 1.36 – 1.80 (m, 10H), 1.80 – 1.99 (m, 2H), 2.36 – 2.82 (m, 4H), 2.86 (dd, 2J = 12.4 Hz, 3J = 4.1 Hz, 1H), 3.76 (dd, 2J = 8.6 Hz, 3J = 6.1 Hz, 1H), 3.87 (s, 3H), 3.87 (s, 6H), 3.89 (s, 3H), 4.07 (dd, 2J = 8.6 Hz, 3J = 6.3 Hz, 1H), 4.16 (dd, 2J = 11.3 Hz, 3J = 7.0 Hz, 1H), 4.37 (dd, 2J = 11.2 Hz, 3J = 6.9 Hz, 1H), 4.80 (d, 2J = 6.4 Hz, 1H), 6.66 – 6.90 (m, 6H).

^13C NMR (50 MHz, CDCl3): δ 26.4, 28.4, 30.9, 33.3, 42.7, 45.2, 49.3, 56.0, 62.5, 72.8, 83.1, 109.0, 111.1, 111.4, 112.0, 118.2, 120.6, 132.7, 135.1, 147.6, 148.6, 149.1, 149.2, 176.9.
NMR-Spectra

$^1$H & $^{13}$C-NMR spectra of compound 2a
$^1$H & $^{13}$C-NMR spectra of compound 2b
$^1\text{H} \& ^{13}\text{C}$-NMR spectra of compound 2c
$^1$H & $^{13}$C-NMR spectra of compound 6a
$^1$H & $^{13}$C-NMR spectra of compound 6b
$^1$H & $^{13}$C-NMR spectra of compound 6c
$^1$H & $^{13}$C-NMR spectra of compound 7a
$^1$H & $^{13}$C-NMR spectra of compound 7b
$^1$H & $^{13}$C-NMR spectra of compound 7c
$^1$H & $^{13}$C-NMR spectra of compound 7d
$^1$H & $^{13}$C-NMR spectra of compound 7e
$^1$H & $^{13}$C-NMR spectra of compound 7f
$^1$H & $^{13}$C-NMR spectra of compound 7g
$^1$H, $^{13}$C-NMR, HSQC, and HMBC spectra of compound 1a (Leoligin)
$J$-mod $^{13}$C NMR (100 MHz, CDCl$_3$)
Heteronuclear Multiple-Bond Correlation (HMBC) spectrum of synthetic leoligin 1
Comparison between the $^{13}$C-NMR shifts of natural product isolate of leoligin$^{13}$, our synthetic leoligin, and the “leoligin” synthesized by Xia et al.$^{14}$

<table>
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<th>Leoligin natural product isolate</th>
<th>Synthetic leoligin of this work</th>
<th>Shifts of &quot;leoligin&quot; reported by Xia</th>
<th>Comparison natural vs. our synthetic</th>
<th>Comparison natural vs. Xia</th>
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<td>8.5</td>
<td>&gt;1.0 deviation</td>
</tr>
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<td>148.3</td>
<td>0.1</td>
<td>0.4</td>
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<td>149</td>
<td>0.1</td>
<td>0.2</td>
<td>0-0.2 deviation</td>
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<tr>
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<td>-0.3</td>
<td>0-0.2 deviation</td>
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Colour code:
- 0-0.2 deviation
- 0.3-1.0 deviation
- >1.0 deviation
- peak missing
$^1$H & $^{13}$C-NMR spectra of compound 1b
$^1$H & $^{13}$C-NMR spectra of compound 1c
$^1$H & $^{13}$C-NMR spectra of compound 1d
$^1$H & $^{13}$C-NMR spectra of compound 1e
$^1$H & $^{13}$C-NMR spectra of compound 1f
$^1$H & $^{13}$C-NMR spectra of compound 1g
$^1$H & $^{13}$C-NMR spectra of compound 1h
$^1$H & $^{13}$C-NMR spectra of compound 1i
$^1$H & $^{13}$C-NMR spectra of compound 1j
$^1$H & $^{13}$C-NMR spectra of compound 1k
$^1$H & $^{13}$C-NMR spectra of compound 1l
Experimental Section Pharmacological Evaluation

This section contains the materials and methods which were used in the cell-based *in vitro* models for the pharmacological evaluation of leoligin and its (synthetic) analogs as well as a table of the obtained data.

**NF-κB Activity**

As described previously, HEK293/NF-κB-luc cells (RC0014, Panomics) were cultured at 37 °C under CO₂ atmosphere (5 %) in DMEM, supplemented with hygromycin B (100 μg / mL), benzylpenicillin (100 U / mL), streptomycin (100 μg / mL), L-glutamine (2 mM) and FBS (10 %). Cells were stained for 1 h in serum-free medium supplemented with Cell Tracker Green CMFDA (C2925, 2 μM, Invitrogen; as this fluorescent probe is retained inside living cells, it was used to monitor cell membrane integrity to quantify the number of viable cells). Then, the cells were re-seeded in 96-well plates (4 × 10⁴ cells per well) in phenol red-free and FBS-free DMEM overnight. After that, cells were pre-treated with test compounds or with the solvent vehicle DMSO (0.1 %) for 30 min and subsequently stimulated with TNFα (2 ng / mL) for 4 h. Cells were then lysed in a luciferase lysis buffer (E1531, Promega) and the luminescence of the firefly luciferase and the fluorescence of the Cell Tracker Green CMFDA were quantified (excitation wavelength: 485 nm; emission wavelength: 520 nm) with a Tecan GENios Pro plate reader (Tecan Group Ltd.). For quantification of the NF-κB activity, the luciferase-derived signal of the NF-κB reporter was normalized by the Cell Tracker Green CMFDA-derived fluorescence, accounting for differences in cell number. Potential differences in cell viability were detected by comparing the Cell Tracker Green CMFDA fluorescence of the solvent vehicle-treated cells and the cells treated with the compounds to be tested. Parthenolide (as a known NF-κB inhibitor) was used as positive control.

**Vascular Smooth Muscle Cell (VSMC) Proliferation**

VSMC proliferation was quantified as previously described. Viable rat aortic VSMCs (0.5 × 10⁴ cells per well) were seeded in growth medium (DMEM/F12 medium containing serum (20 %), gentamicin (30 μg / mL) and amphotericin (15 ng / mL)) in 96-well plates. After 24 h, the medium was removed, cells were washed once with starvation medium (DMEM/F12 medium containing serum (0.1 %), BSA (0.2 %), gentamicin (30 μg / mL) and amphotericin (15 ng / mL)) and incubated in starvation medium for another 24 h. Quiescent cells were then pre-treated for 30 min with the compounds to be tested and then induced to proliferate with PDGF (20 ng/mL). Unstimulated cells were used for normalization and assessing of the basal level of proliferation. The final concentration of the solvent vehicle DMSO was identical (0.1 %) in all wells. After 48 h, VSMC proliferation was quantified by conversion of the dye resazurin for 2 h. Fluorescence was measured at 580 nm, with excitation at 535 nm in a Tecan GENios Pro plate reader (Tecan Group Ltd.) as described previously.

**Endothelial Cell (EC) Proliferation**

As previously described, to estimate EC proliferation human umbilical vein ECs (0.5 × 10⁴ cells per well; immortalized as described) were seeded in 96-well plates for 24 h in HUVEC Complete Medium
(200 µL per well, EBM growth medium supplemented with FBS (10 %), EBM SingleQuots (Lonza), benzylpenicillin (100 U / mL), streptomycin (100 µg / mL), and amphotericin (1 %)). Then the medium was exchanged with fresh HUVEC Complete Medium and the cells were treated with the compounds to be tested for 48 h. Then the medium was removed, cells were washed once with PBS (200 µL) and treated with HUVEC Complete Medium (150 µL), containing resazurin (10 µg / mL), for 2 h. The fluorescence was measured at 580 nm, with excitation at 535 nm in a Tecan GENios Pro plate reader (Tecan Group Ltd.) as described previously.\textsuperscript{18}

Cytotoxicity

Potential cytotoxic effects on VSMCs were determined as previously described.\textsuperscript{19} Rat aortic VSMCs (5 × 10\textsuperscript{3} cells per well) were seeded in 96-well plates. After 24 h, the cells were serum-starved for another 24 h to render them quiescent. The cells were then pre-treated for 30 min with the compounds to be tested or with the solvent vehicle DMSO (0.1 %), and then stimulated for 24 h with PDGF-BB (20 ng / mL). The loss of cell membrane integrity as an indication of cell death\textsuperscript{21-22} was then quantified by the release of lactate dehydrogenase (LDH). For this, the supernatant of the cells was assessed for LDH activity. For assessment of total LDH activity, identically treated samples were incubated for 45 min in the presence of Triton X-100 (1 %). Enzyme activity in both cases was measured for 30 min in the presence of L-lactic acid (4.5 mg / mL), NAD\textsuperscript{+} (0.56 mg / mL), diaphorase (1.69 U / mL), BSA (0.004 w/v %), D-sucrose (0.15 w/v %) and INT (0.5 mM) in the dark. Enzyme activity was halted with oxamic acid (1.78 mg / mL) and the absorbance was measured at 490 nm. Effects on cell viability were calculated as percentage of extracellular LDH enzyme activity. Digitonin (50 µg/mL), a natural product with known membrane-disrupting activity, was used as a positive control.

Statistical Analysis

Statistical analysis and determination of IC\textsubscript{50} values was conducted using GraphPad PRISM (version 4.03, GraphPad Software Inc.).
## Dataset of the pharmacological evaluation of furan-type lignans

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Cmpd.</th>
<th>VSMC inhibition: IC\textsubscript{50} / μM</th>
<th>EC inhibition: Residual signal / %\textsuperscript{a,b}</th>
<th>NF-κB inhibition: IC\textsubscript{50} / μM</th>
<th>VSMC cytotoxicity: Extracellular LDH / %\textsuperscript{d}</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>1a</td>
<td>32.1</td>
<td>51 ± 5 ***&lt;br&gt;55 ± 6 ***</td>
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<td>87 ± 3\textsuperscript{e} 3.1 ± 0.7 n.s.</td>
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<tr>
<td><img src="image2.png" alt="Chemical Structure" /></td>
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<td>EC inhibition: Residual signal / %a,b</td>
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<td>signal / %c viability</td>
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<td>EC inhibition: Residual signal / %a, b</td>
<td>NF-κB inhibition: IC50 / μM</td>
<td>SMC cytotoxicity: Extracellular LDH / %d</td>
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<td>EC inhibition: Residual signal / %&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>NF-κB inhibition: IC50 / μM</td>
<td>SMC cytotoxicity: Extracellular LDH / %&lt;sup&gt;d&lt;/sup&gt;</td>
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**Notes:**

- <sup>a</sup> ANOVA / Bonferroni (***: p < 0.001; **: p < 0.01; *: p < 0.05; n.s.: not significant).
- <sup>b</sup> Single-dose value, measured at 30 μM: given is the residual signal (of compound-treated cells ± standard error of the mean) in % relative to untreated (100 %) cells.
- <sup>c</sup> Single-dose value, measured at 20 μM: given is the viability signal (of stimulated and compound treated cells ± standard error of the mean) in % relative to stimulated but untreated (100 %) cells.
- <sup>d</sup> Single-dose value, measured at 30 μM: given is the ratio of extracellular lactate dehydrogenase (of compound-treated cells ± standard deviation) in % relative to untreated (≤ 5 %) cells.
Literature References