Unravelling stereoisomerism in the acid catalysed lignin conversion: an integration of experimental trends and theoretical evaluations

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S1.0 Analytical procedures

High-performance liquid chromatography (HPLC) was performed on a Shimadzu prominence system equipped with a photodiode detector (Shimadzu SPD-M20A Prominence). The column is Agilent Eclipse XDB-C18 5 Column (5 μm 4.6 × 150 mm). Data analysis was processed with Shimadzu Lab Solutions Version 5.51 software. 1,2,4,5-tetramethylbenzene was used as an internal standard. All samples were run using MeCN (0.1% formic acid) (A)/H_2O (0.1% formic acid) (B) gradient follow with a flow rate of 1.0 mL/min. The method started with 5% A/95% B for 10 min followed by a gradient to 95% A/5% B over 30 min followed by 10 min at 95% A/5% B followed by a gradient to 5% A/95% B over 5 min followed by 5 min at 5% A/95% B a flow rate of 1.0 mL/min.

Preparative High-Performance Liquid Chromatography was performed on a Shimadzu prominence system equipped with a photodiode detector (Shimadzu SPD-M20A Prominence), and a FRC-10A fraction collector was used. The column is Xbridge BEH130 Prep C18 Column (10 μm, 10 × 150 mm). Data analysis was processed with Shimadzu Lab Solutions Version 5.51 software. Samples were run using MeCN (0.1% formic acid) (A)/H_2O (0.1% formic acid) (B) in a ratio of 20% A/80% B for 30 min following by a flow rate of 1.0 mL/min.

Ultra-high performance liquid chromatography-mass spectrometry (UPLCMS) was performed using a Waters Acquity Ultra Performance LC system equipped with a TQ detector and an Acquity UPLC HSS T3 Column (1.8 μm 2.1 × 150 mm). Analysis was performed using MassLynx V4.1 software.

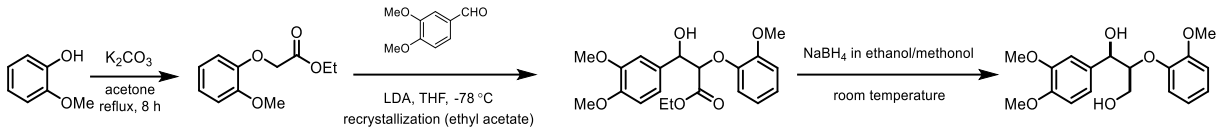
Gas chromatography-mass spectrometry (GC-MS) was performed using an Agilent 6890 series GC system equipped with a HP973 mass detector with helium as carrier gas.

NMR: NMR spectra were recorded on a Varian Oxford Mercury AS 400, an Agilent Technologies 400/54 Premium shielded spectrometer or a Bruker Ascend 600 using $CDCl_3$ or DMSO-d_6 as solvent at room temperature. Chemical shift values are reported in part per million (ppm) with the solvent resonance as the internal standard. Data report followed the bellowing pattern: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants (Hz), and integration.

Thin layer chromatography was performed on pre-coated aluminum plates (60/kieselguhr F_{254} Merk) and visualized under UV light (254 nm) or by staining with $KMnO_4$.

S 2.0 Synthesis of standard compounds

Compound **A**: Ethyl 3-(3,4-dimethoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propanoate



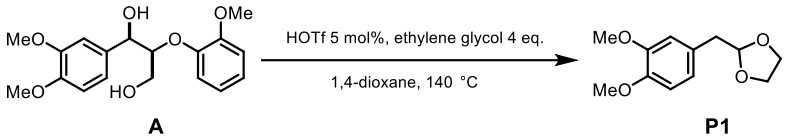
Compound **A** was synthesized following a literature procedure.[1] Column purification results in **A** dominantly in the *erythro* configuration (> 97%, determined by NMR).

Compound **A** in the *erythro* configuration:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.03 (m, 1H), 7.01–6.87 (m, 5H), 6.84 (d, *J* = 8.2 Hz, 1H), 4.98 (d, *J* = 4.6 Hz, 1H), 4.16 (m, 1H), 3.98–3.83 (m, 10H), 3.66 (dd, *J* = 12.2, 3.4 Hz, 1H).

Spectral data were consistent with the values reported in literature.[1]

Compound **P1**: 2-(3,4-dimethoxybenzyl)-1,3-dioxolane



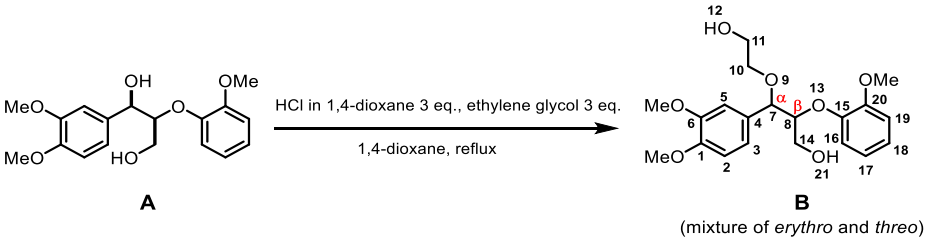
A **P1**

Substrate (e.g., compound **A** in the *erythro* configuration, 50 mg, 0.15 mmol) was placed in a 20 mL microwave vial, equipped with a magnetic stirring bar. Solvent (1,4-dioxane, 10 mL) and ethylene glycol (37 mg, 0.6 mmol, 4 eq.) were added and the vial was sealed. The solution was stirred and heated to 140 °C. HOTf (5 mol%, 50 µL, from a 0.15 mmol/mL stock solution in 1,4-dioxane) was added by syringe with a thin needle through the septum of the microwave vial. The reaction was stirred at 140 °C for 15 min before being cooled rapidly in an ice bath and quenched with a drop of trimethylamine, transferred to a round bottomed flask and concentrated in *vacuo*. Purification was carried out via column chromatography (20–50% EtOAc/heptane) yielding the product as an off white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 3H, Ar-H), 5.04 (t, *J* = 4.8 Hz, 1H), 3.98–3.93 (m, 2H), 3.88 (s, 3H), 3.87–3.82 (m, 5H), 2.91 (d, *J* = 4.8 Hz, 2H).

Spectral data were consistent with the values reported in literature.[2]

Compound **B**: 3-(3,4-dimethoxyphenyl)-3-(2-hydroxyethoxy)-2-(2-methoxyphenoxy)propan-1-ol



A **B**
(mixture of *erythro* and *threo*)

Substrate **A** in *erythro* configuration (100 g, 0.2991 mmol) was dissolved in 1,4-dioxane (5 mL) and EG (5 mL). 3 eq. of HCl (from a 4N HCl in 1,4-dioxane solution) was added to the mixture and the reaction refluxed for 2 h, after which no more starting material was visible by TLC. The reaction was quench by addition of 10 mL sat. aqueous $NaHCO_3$ and extracted into EtOAc. The organic layers were combined and washed with brine and dried over $MgSO_4$ prior to being filtered and concentrated in *vacuo*. The crude product was purified via column chromatography (30–60% Acetone/PET Ether) to obtain the product as a clear semi-solid. The isomer mixture of **B** was further separated by preparative HPLC as fraction 1 (*threo*) and fraction 2 (*erythro*), which was confirmed by comparing the typical coupling constant between H_α and H_β with literature.[3-6]

Ethylene glycol adduct in *threo* configuration:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.16 (d, 1H, H3), 7.03–7.01 (m, 1H, Ar-H), 6.96–6.89 (m, 4H, Ar-H), 6.86 (d, 1H, Ar-H), 4.64 (d, *J* = 7.7 Hz, 1H, H7), 4.25 (m, 1H, H8), 3.91–3.86 (m, 9H, 3x -OCH3), 3.74–3.64 (m, 2H, H11), 3.61–3.56 (m, 1H, H10), 3.53–3.40 (m, 3H, H14 and H10).

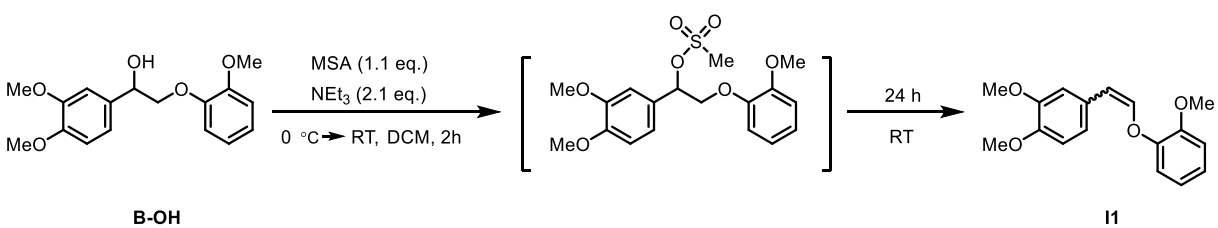
^{13}C NMR (151 MHz, $CDCl_3$) δ 151.0, 149.5, 149.3, 148.5 (C4 or C15), 130.7 (C4 or C5), 123.6, 121.7, 120.2, 119.8 (C3), 112.3, 111.2, 110.1 (C4 or C5), 87.2 (C8), 82.9 (C7), 70.6, 61.9 (C11), 61.7 (C14), 56.2 (-O<u>C</u>H$_3$), 56.1 (-O<u>C</u>H$_3$), 56.0 (-O<u>C</u>H$_3$).

Ethylene glycol adduct in *erythro* configuration:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.01–6.94 (m, 3H, Ar-H), 6.89–6.84 (m, 2H, Ar-H), 6.80–6.76 (m, 1H, Ar-H), 6.57 (dd, 1H, Ar-H), 4.70 (d, *J* = 7.1 Hz, 1H, H7), 4.11 (m, 1H, H8), 3.99 (dd, 1H, H14), 3.88 (s, 3H, -OCH$_3$), 3.87 (s, 3H, -OCH$_3$), 3.83 (s, 3H, -OCH$_3$), 3.81–3.76 (m, 2H, H11 and H14), 3.75–3.70 (m, 1H, H11), 3.70–3.64 (m, 1H, H10), 3.51–3.45 (m, 1H, H10).

^{13}C NMR (151 MHz, $CDCl_3$) δ 151.5, 149.3, 149.0, 147.3, 131.8, 123.8, 121.5, 120.2, 120.1, 112.3, 111.1, 110.4, 86.6 (C8), 80.6 (C7), 70.7 (C10), 61.9 (C11), 61.1 (C14), 56.2 (-O<u>C</u>H$_3$), 56.1 (-O<u>C</u>H$_3$), 56.0 (-O<u>C</u>H$_3$).

Compound **I1**: 1,2-dimethoxy-4-(2-(2-methoxyphenoxy)vinyl)benzene



B-OH **I1**

1-(3,4-Dimethoxyphenyl)-2-(2-methoxyphenoxy)ethan-1-ol (**B-OH**) was synthesized following the literature procedure.[7] To a DCM (5 mL) solution of **B-OH** (100 mg, 0.329 mmol), cooled to 0 °C, was added methanesulfonic anhydride (MSA = 63 mg, 0.361 mmol, 1.1 eq.) and trimethylamine (0.1 mL, 2.1 eq.). The resulted mixture was stirred at 0 °C for 30 min and then allowed to warm up to room temperature. After stirring overnight, the reaction mixture was diluted with water (5 mL) and extracted with DCM. The organic phase was successively washed with 10 mL of a 1 M HCl solution, brine (15 mL), then dried over $MgSO_4$. The solvent was removed under reduced pressure. The product was purified by column chromatography (pentane/acetone = 97/3) to obtain a *cis*/*trans* isomer mixture (*cis*/*trans* = 7.7/1). The ratio obtained by quantitative proton NMR was used for HPLC calibration of the separate isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 2.0 Hz, 1H), 7.16–7.04 (m, 3H), 7.02 (d, *J* = 12.5 Hz, 0.115H, *trans*), 7.00–6.91 (m, 2H), 6.87–6.80 (m, 1H), 6.55 (d, *J* = 6.8 Hz, 0.885H, *cis*), 6.29 (d, *J* = 12.5 Hz, 0.115H, *trans*), 5.56 (d, *J* = 6.8 Hz, 0.885H, *cis*), 3.91 (s, 3H), 3.89 (s, 6H).

Spectral data were consistent with the values reported in literature.[7]

S 3.0 Typical procedure for the time course reaction

A typical procedure for the time course reaction was followed as used in our previous investigation.[8] Compound **A** (2 mL of a 0.15 mmol stock solution in 1,4-dioxane) was added to 20 mL pressure vial equipped with a magnetic stirring bar. Internal standard (1,2,4,5-tetramethylbenzene, 3 mL of a 0.3 mmol stock solution in 1,4-dioxane) was added. Ethylene glycol (0.7 mL of a 0.6 mmol stock solution in 1,4-dioxane) was added, and the vial was sealed. The solution was stirred and heated to the desired temperature. An initial time point sample was taken immediately prior to the catalyst addition. The catalyst, $Yb(OTf)_3$, (e.g. 10 mol%, 0.3 mL, 0.015 mmol from a stock solution in 1,4-dioxane) was added by syringe with a thin needle through the septum of the pressure vial. 0.1 mL samples were taken from the vial through the septum with a thin needle at intervals over a 24 h period and quenched onto HPLC sample vials containing 0.9 mL of a 60:40 MeCN:H_2O solution basified with Et_3N. The samples were then analyzed by HPLC. The temperatures reported in the manuscript are referred to as internal temperatures of the reaction mixture unless otherwise stated.

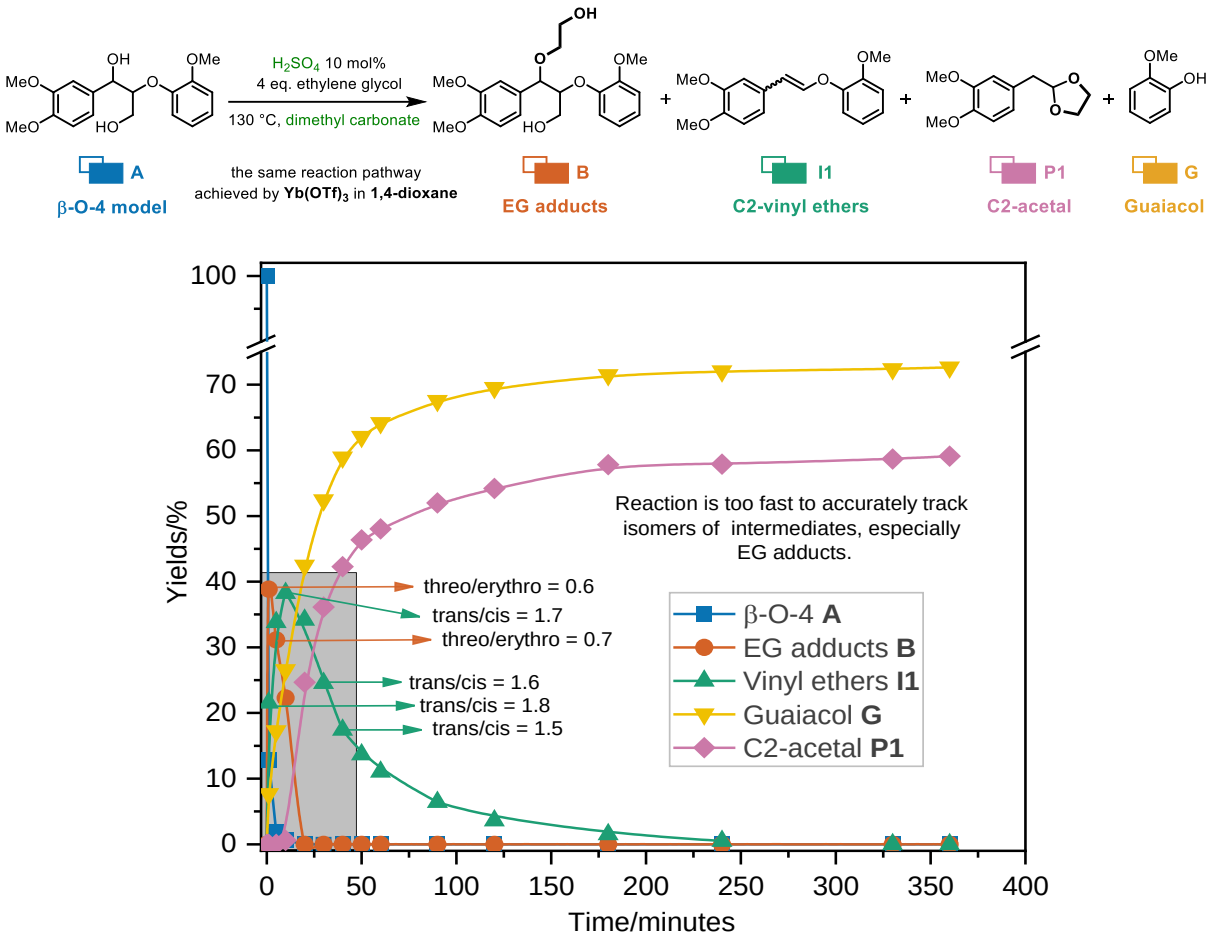


Fig. S1 Graph of time course of the reaction of β-O-4 model compound **A** with 10 mol% H_2SO_4, 4 eq. ethylene glycol, in dimethyl carbonate at 130 °C. Yields were obtained via HPLC analysis using 1,2,4,5-tetramethylbenzene as internal standard.

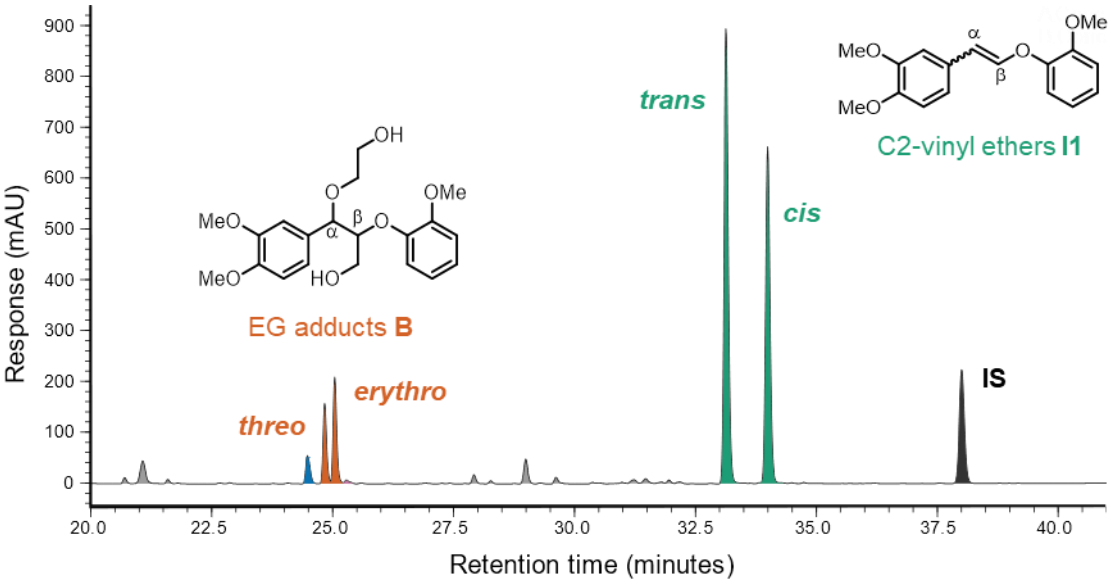


Fig. S2 HPLC chromatogram of the diol-stabilized acidolysis at 20 min and the identified intermediates peaks. Reaction condition: 10 mol% $Yb(OTf)_3$, 4 eq. ethylene glycol, in 1,4-dioxane at 120 °C using 1,2,4,5-tetramethylbenzene as internal standard (IS).

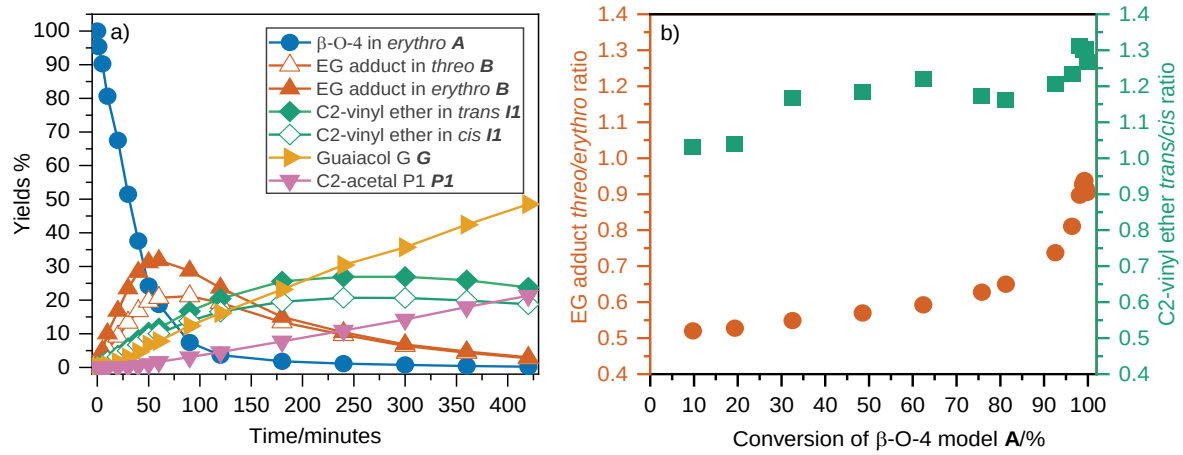


Fig. S3 a) Evolution of the reaction of the non-phenolic model compound **A** with 10 mol% $Zn(OTf)_2$, 4 eq. ethylene glycol, in 1,4-dioxane at 130 °C. Yields were obtained via HPLC analysis using 1,2,4,5-tetramethylbenzene as an internal standard. b) The change of *threo/erythro* ratio of EG adduct **B** and *trans*/*cis* ratio of vinyl ether **I1** along conversion of **A**.

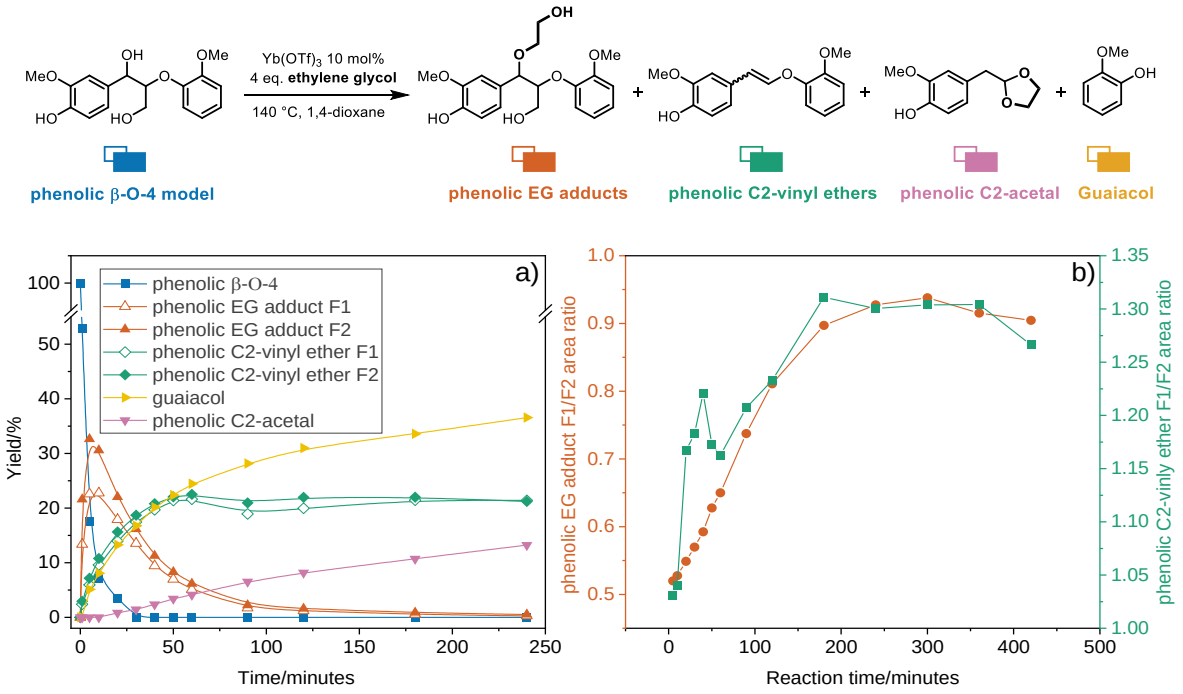


Fig. S4 a) Evolution of the reaction of the phenolic β-O-4 model compound with 10 mol% $Yb(OTf)_3$, 4 eq. ethylene glycol, in 1,4-dioxane at 130 °C. Yields were obtained via HPLC analysis using 1,2,4,5-tetramethylbenzene as an internal standard. b) The change of F1/F2 area ratio of phenolic EG adduct and F1/F2 area ratio of phenolic vinyl ether along reaction time. Yields are estimated with the response factors of their non-phenolic counterparts.

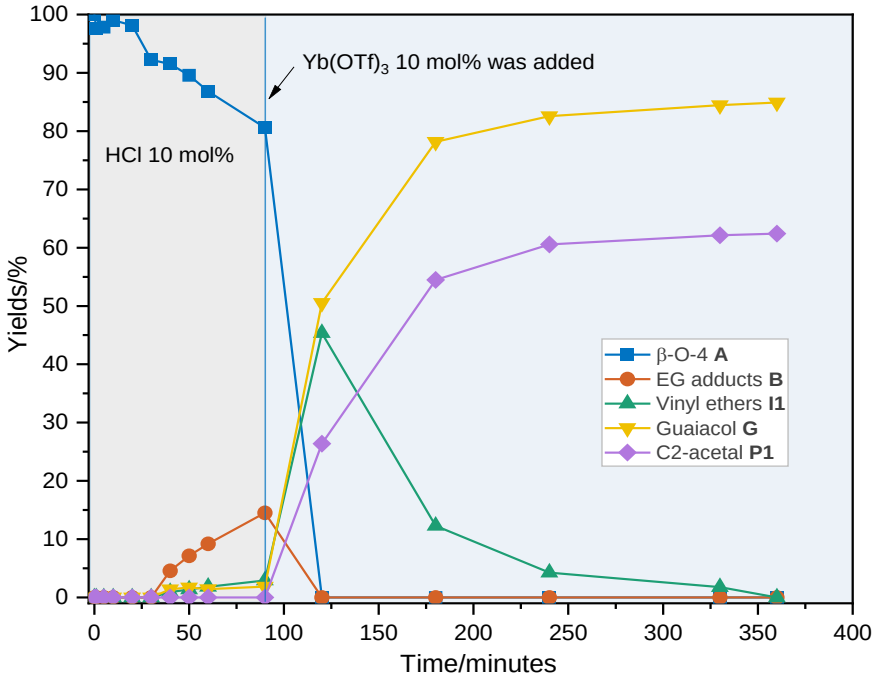


Fig. S5 Evolution of the reaction of the non-phenolic model compound **A** with 10 mol% HCl, 4 eq. ethylene glycol, in 1,4-dioxane at 130 °C. After 90 min, 10 mol% $Yb(OTf)_3$ was added. Yields were obtained via HPLC analysis using 1,2,4,5-tetramethylbenzene as the internal standard.

S 4.0 Multi-scale modeling

The torsional angles of the main chain, connecting the two rings, and those of the side chains, were analyzed to classify the structures and displayed as energy contour plots or mere distributions in the case of the side moieties (see Fig. S1–S3).

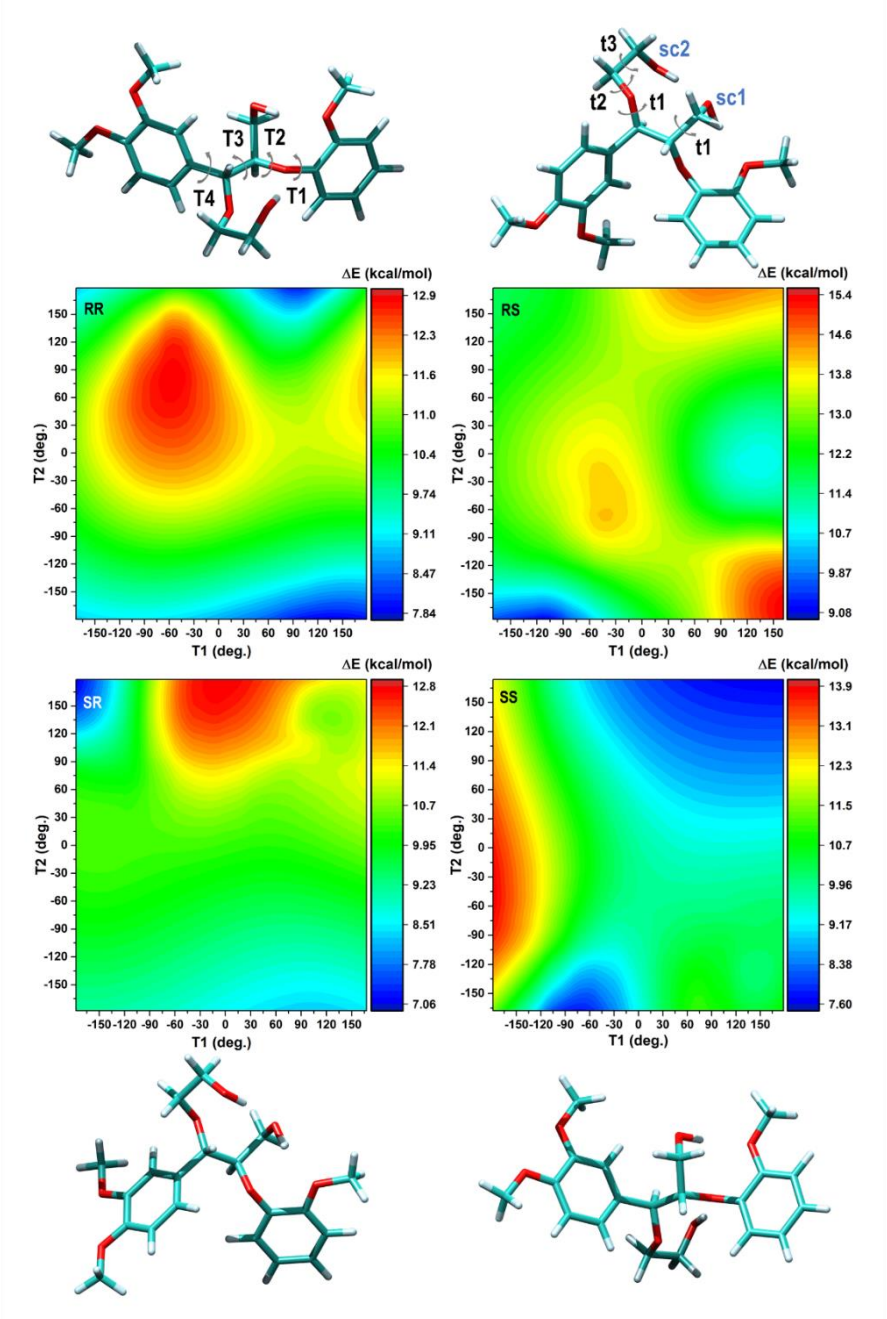


Fig. S6 Minimum energy structures of the EG adducts **B** (RR, RS, SR, SS absolute configurations). Contour plots of the (T1, T2) pairs are colored according to the energy difference relative to the lowest energy structure.

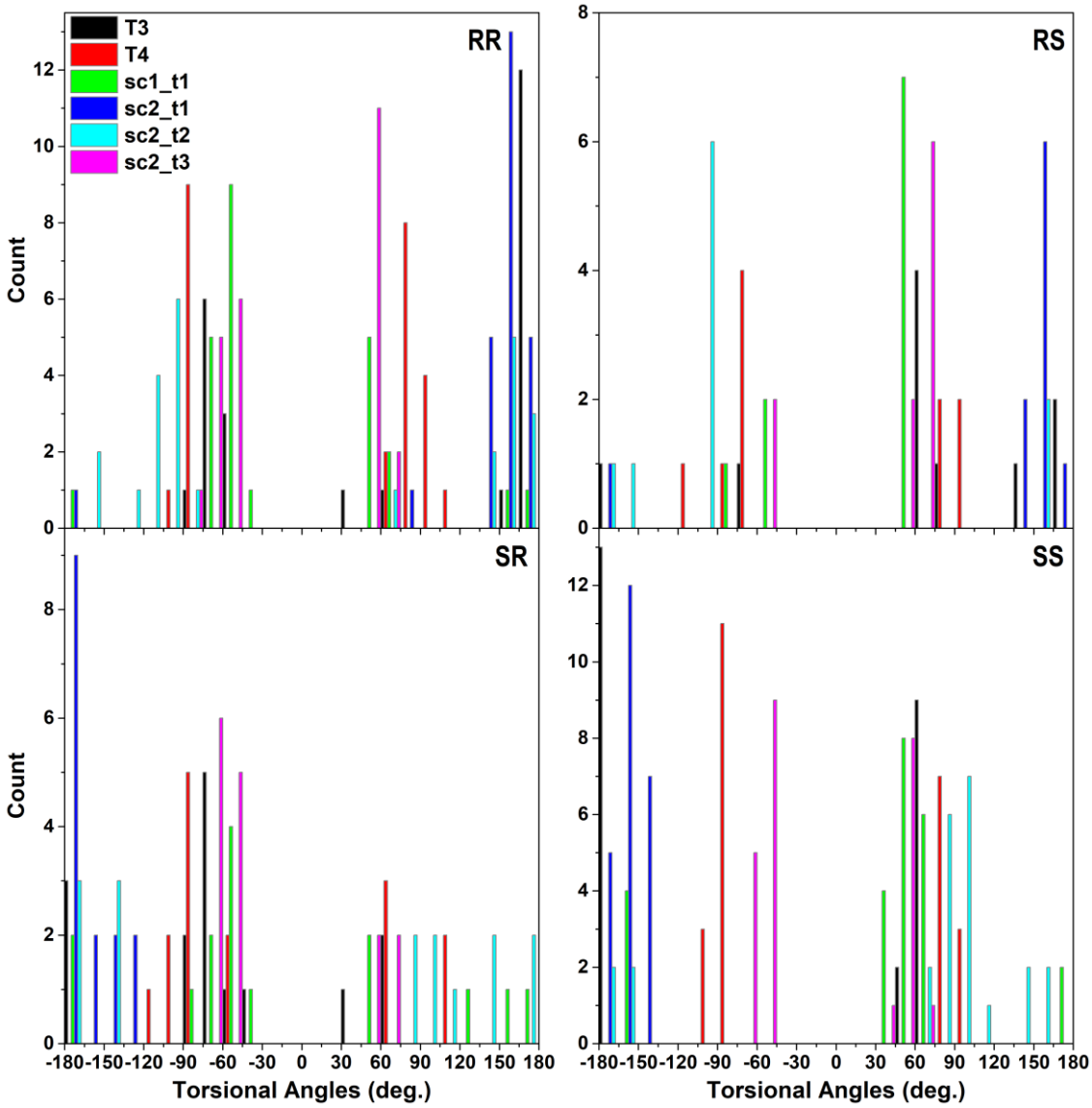


Fig. S7 T3, T4, and side chains dihedral angle distributions of the optimized structures of the EG adduct **B** (RR, RS, SR, SS absolute configurations).

Table S1: Dihedral angles of the lowest energy minima of the EG adducts **B**.

Conf.	T1 (deg.)	T2 (deg.)	T3 (deg.)	T4 (deg.)	sc1_t1 (deg.)	sc2_t1 (deg.)	sc2_t2 (deg.)	sc2_t3 (deg.)
RR-*threo*	102.76	159.18	170.92	-82.25	-58.91	148.63	-99.13	59.22
RS-*erythro*	103.08	-153.45	72.95	-74.66	53.78	152.00	-92.35	66.17
SR-*erythro*	101.47	157.84	-71.32	-99.59	-55.56	-153.40	92.69	-66.18
SS-*threo*	102.45	-156.95	-169.57	81.86	58.02	-146.92	97.19	-60.68

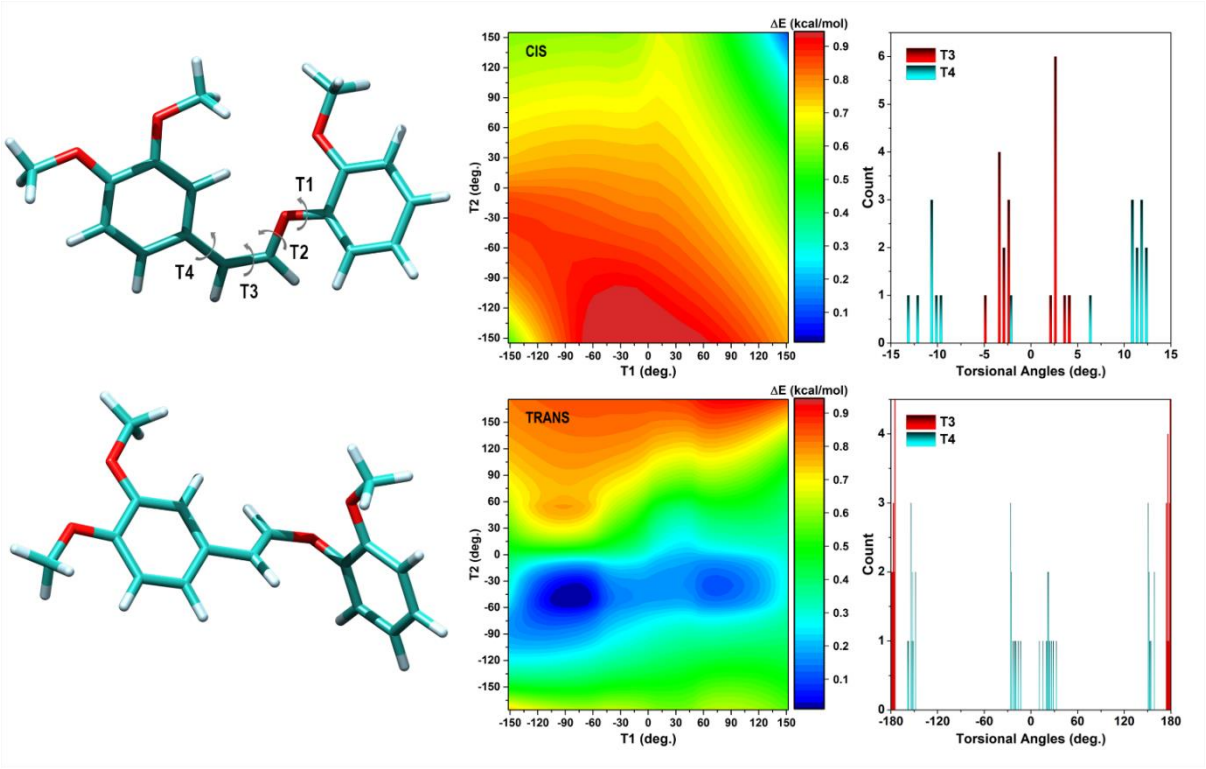


Fig. S8 Minimum energy structures of the vinyl ethers **I1** in the *cis* and *trans* conformations (top and bottom pictures, respectively). Contour plots of the (T1, T2) pairs are colored according to the energy difference relative to the lowest energy structure. T3 and T4 dihedral angle distributions are also displayed (left-hand-side).

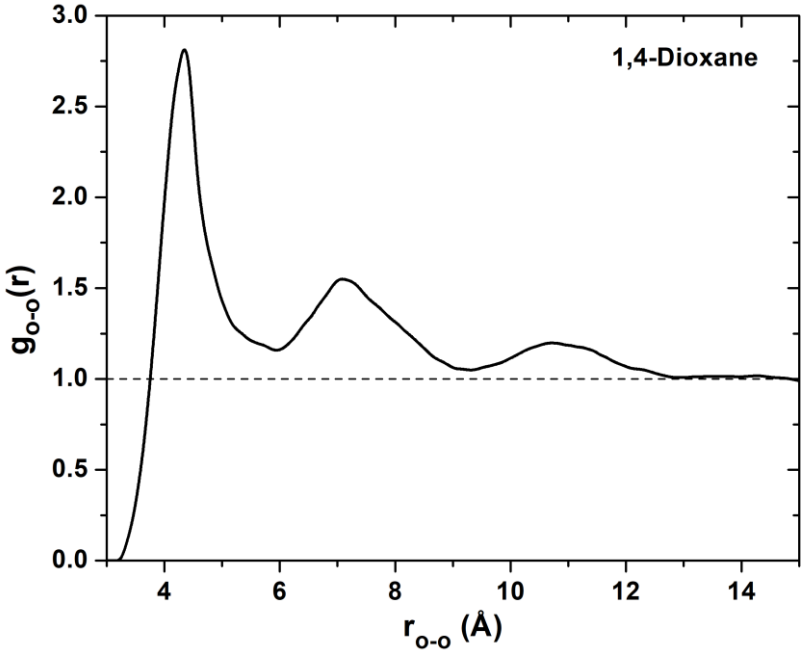


Fig. S9 Radial distribution functions corresponding to Odiox–Odiox pairs.

S 5.0 Separate calibration curves for ethylene glycol B adducts and vinyl ethers I1

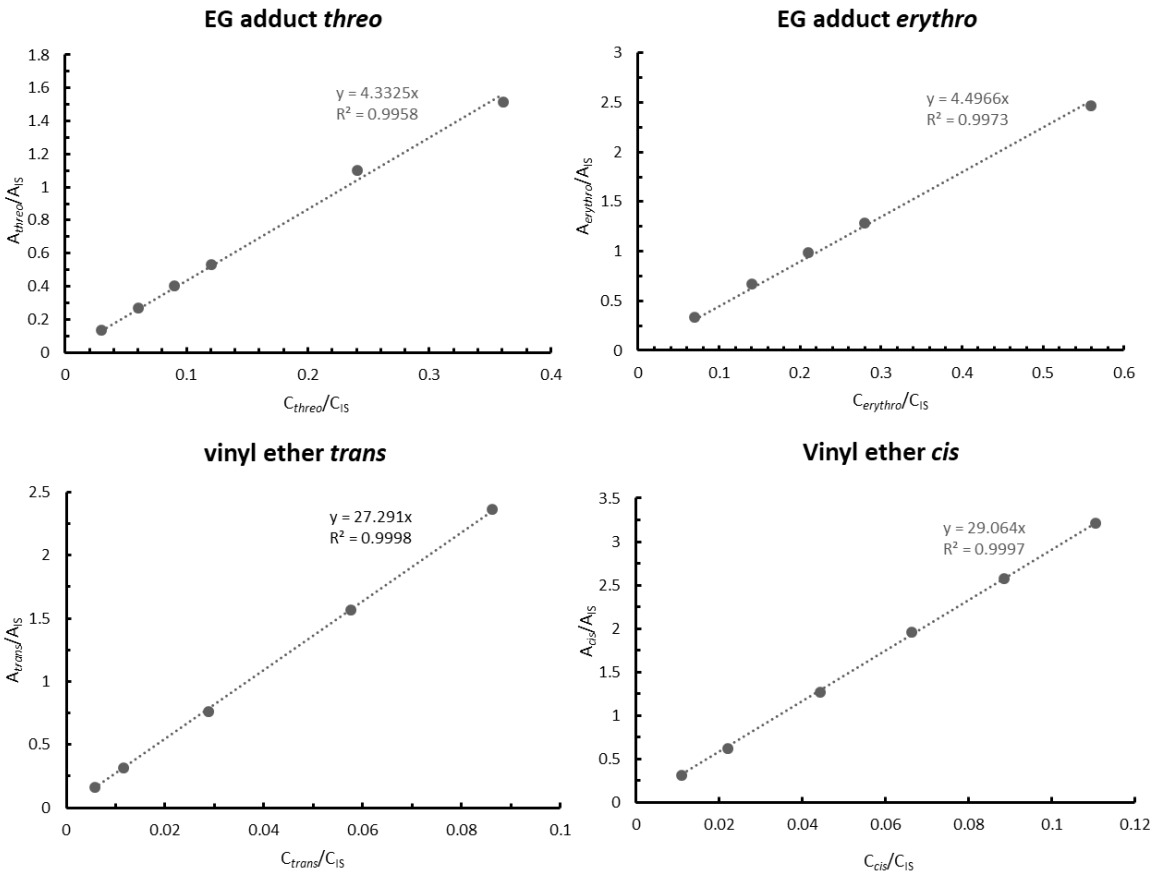
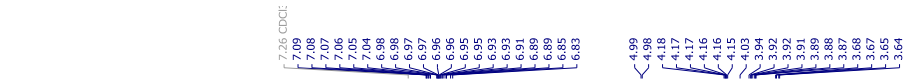
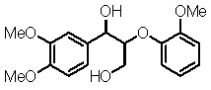


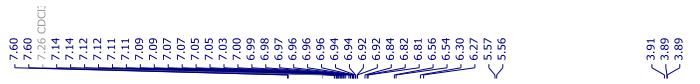
Fig. S10 Calibration curve for ethylene glycol adducts **B** and vinyl ethers **I1**.

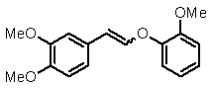
S 6.0 NMRs



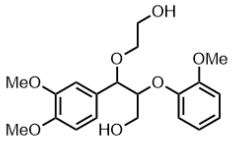


erythro > 97%

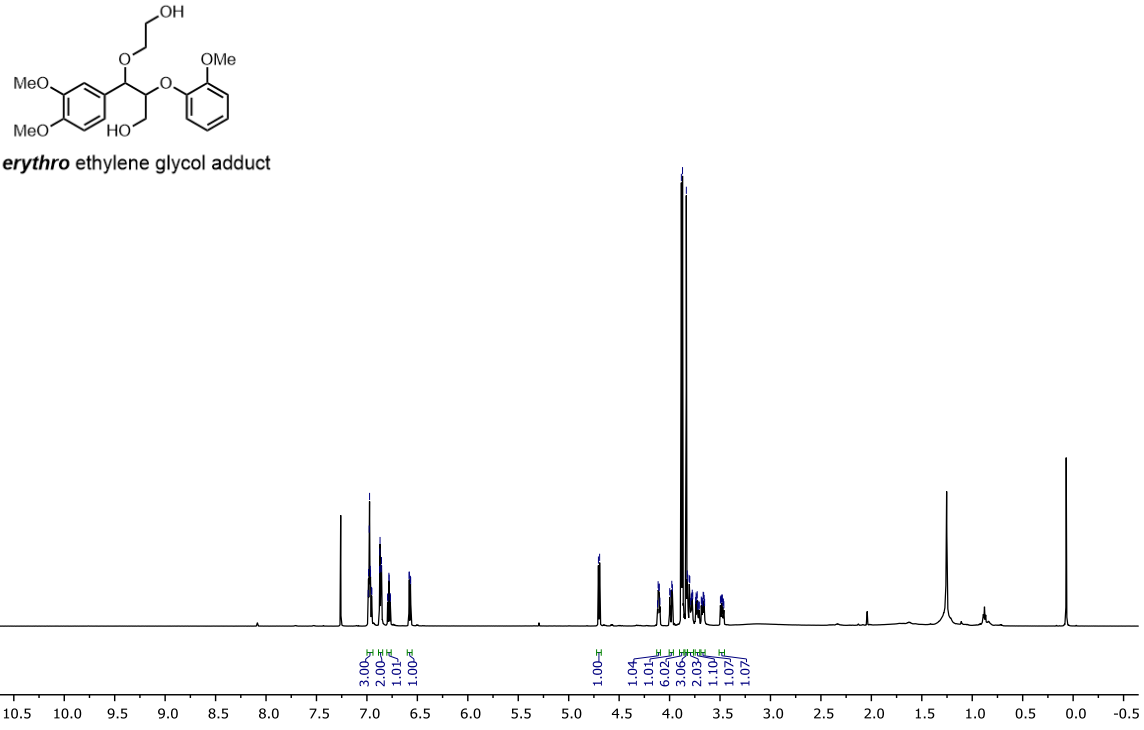




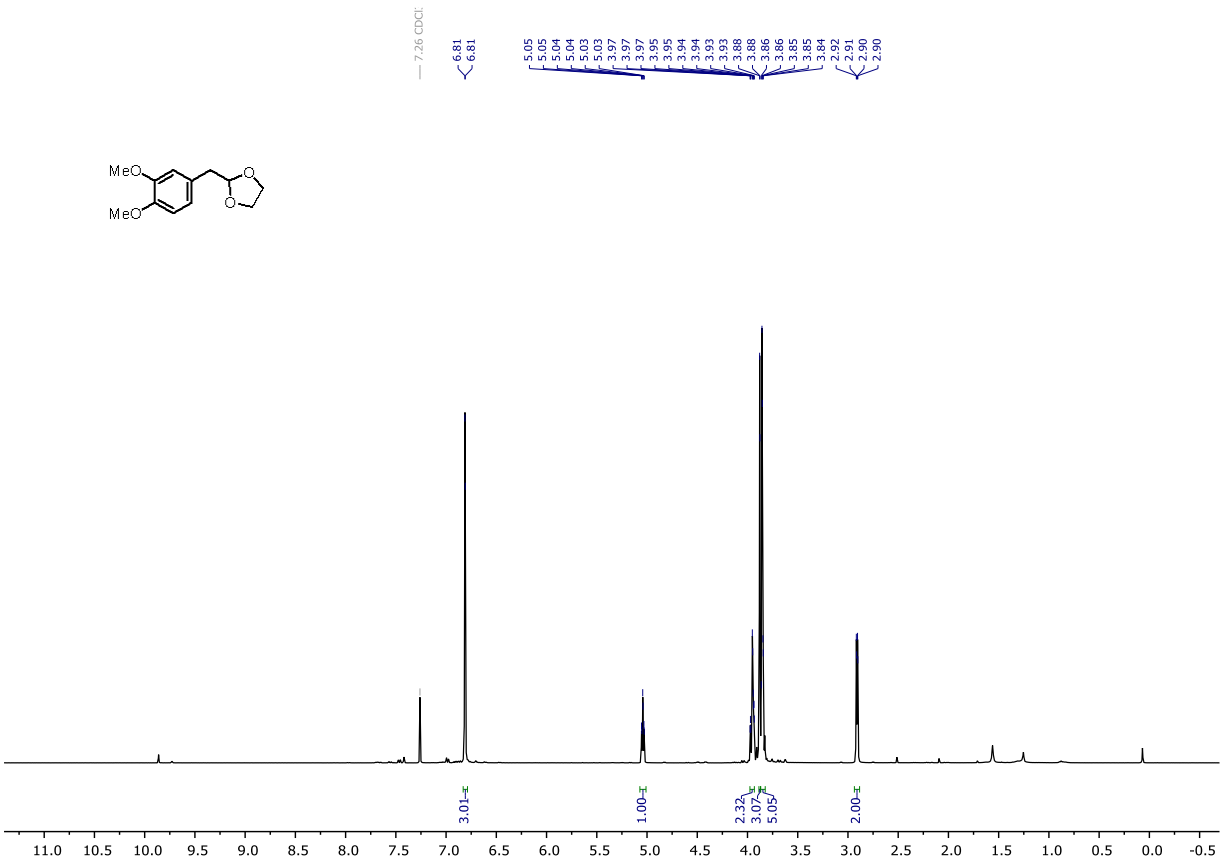
mixture of *trans* and *cis*



threo ethylene glycol adduct



erythro ethylene glycol adduct



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