Apr 07, 2023

Synthetic Procedure of 2-(1-(4-hydroxy-3-methoxyphenyl)propan-2-yl)-6-methoxy-4-propylphenol

DOI
dx.doi.org/10.17504/protocols.io.81wgb6emolpk/v1

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DOI: **https://dx.doi.org/10.17504/protocols.io.81wgb6emolpk/v1**

Protocol Citation: Lisa M Stanley, Rui Katahira, Gregg T. Beckham 2023. Synthetic Procedure of 2-(1-(4-hydroxy-3-methoxyphenyl)propan-2-yl)-6-methoxy-4-propylphenol. **protocols.io**
https://dx.doi.org/10.17504/protocols.io.81wgb6emolpk/v1

Protocol status: Working
We use this protocol and it's working

Created: July 16, 2022

Last Modified: August 22, 2023

Protocol Integer ID: 66809

Keywords: lignin model compounds, dimer, nuclear magnetic resonance, lignin, synthesis, beta-five linkage, degradation reaction pathways of lignin polymer, lignin model compound, dimeric lignin model compound, lignin polymers in biomass, lignin polymer, lignin fraction, typical lignin interunit linkage, lignin, propylphenol, trimeric model compound, biomass, degradation reaction pathway, depolymerization, direct understanding of the degradation reaction pathway, effectiveness of catalyst, synthetic procedure, degree of depolymerization, catalyst

Funders Acknowledgements:
U.S. Department of Energy Office of Energy Efficiency and Renewable Energy Bioenergy Technologies Office
Grant ID: DE-AC36-08GO28308

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This work was authored by the National Renewable Energy Laboratory, operated by Alliance for Sustainable Energy, LLC, for the U.S. Department of Energy (DOE) under Contract No. DE-AC36-08GO28308. Funding provided by U.S. Department of Energy Office of Energy Efficiency and Renewable Energy Bioenergy Technologies Office. The views expressed herein do not necessarily represent the views of the DOE or the U.S. Government.

Abstract

A direct understanding of the degradation reaction pathways of lignin polymers in biomass is difficult due to the complexity of lignin's structure. To overcome the difficulty, simple lignin dimeric and trimeric model compounds which include typical lignin interunit linkages are useful to clarify reaction mechanisms. The following procedure describes the synthetic procedure of a β-5 dimeric lignin model compound: 2-(1-(4-hydroxy-3-methoxyphenyl)propan-2-yl)-6-methoxy-4-propylphenol. Lignin model compounds are useful for screening the effectiveness of catalysts and microoganisms. As well as determining the effect of a treatment on the lignin fraction, in particular the effect on the degree of depolymerization in the lignin polymer.

Materials

Isoeugenol **Merck MilliporeSigma (Sigma-Aldrich) Catalog** #I7206 Step 1.1

Methanol **Merck MilliporeSigma (Sigma-Aldrich) Catalog** #M3641 Step 1.1 and Step 1.2

Citric acid **Merck MilliporeSigma (Sigma-Aldrich) Catalog** #251275 Step 1.1 [see Note 1]

Disodium Hydrogen Phosphate **Merck MilliporeSigma (Sigma-Aldrich) Catalog** #S9763 Step 1.1 [see Note 1]

Horseradish Peroxidase **Catalog** #P8250-25KU Step 1.1

Hydrogen Peroxide **Fisher Scientific Catalog** #H325 Step 1.1

Ethyl Acetate **Fisher Scientific Catalog** #E145 Steps 1.1, 2.1, and 2.2

Sodium Chloride **Fisher Scientific Catalog** #S271 Step 1.1 (see Note 2)

Sodium Sulfate **Merck MilliporeSigma (Sigma-Aldrich) Catalog** #239313 Step 1.1

Palladium on carbon **Merck MilliporeSigma (Sigma-Aldrich) Catalog** #205680 Step 1.2

Hydrochloric acid **Merck MilliporeSigma (Sigma-Aldrich) Catalog** #258148 Step 1.2

Hexane mixture of isomers **Merck MilliporeSigma (Sigma-Aldrich) Catalog** #178918 Steps 2.1 and 2.2

Silica gel **Catalog** #60737 Steps 2.1 and 2.2

Acetone-D6 **Catalog** #DLM-9-25ML Steps 3.1 and 3.2

Troubleshooting

Safety warnings

Almost all chemicals used for this procedure are hazardous. Read the Safety Data Sheet (SDS) for all chemicals and follow all applicable chemical handling and waste disposal procedures.

Before start

All glassware is dried in an oven set to 105ºC then cooled in a desiccator prior to use.

Synthetic Procedure

1

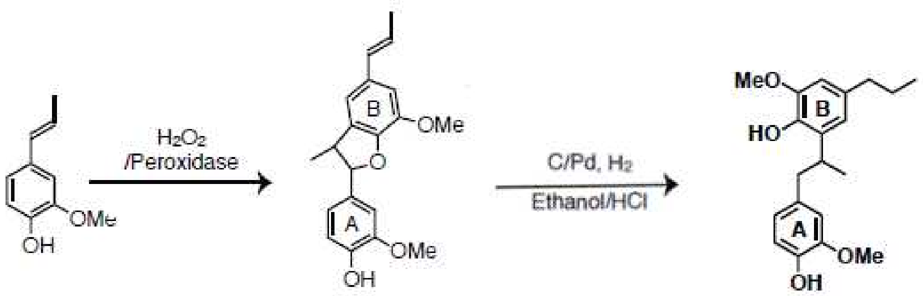

Figure 1. Two-step reaction scheme of 2-(1-(4-hydroxy-3-methoxyphenyl)propan-2-yl)-6-methoxy-4-propylphenol (β-5 dimer).

1.1 A solution of 1480 mL citrate-phosphate buffer (20 mM, pH 3.5) [see Note 1] was heated to 38 °C in a silicone oil bath. A solution of isoeugenol (5.00 mL , 0.0328 mol) in methanol (164 mL) was added in portions with vigorous stirring to the buffer solution. 20 mg horseradish peroxidase (HRP, 2500 U, Type II) was then added to the solution. The mixture was stirred while hydrogen peroxide, H_2O_2, (1.875 mL , 0.0612 mol) was added dropwise over 10 min. The reaction mixture was stirred for an additional 1 h and then filtered using a Büchner funnel. The resulting residue was separated and the funnel was washed with ethyl acetate (EtOAc). The organic solubles and the residue were combined and washed with a saturated solution of brine [see Note 2], and then dried using sodium sulfate (Na_2SO_4).[1,2] The crude product obtained after evaporation of the solvent in vacuo was crystallized from methanol to afford (±)-licarin A (1.3176 g, 24.6%).

Note

Note 1. Preparation of 20 mM citrate-phosphate buffer: 3.84 g Citric acid and 2.84 g disodium hydrogen phosphate are added to 1 L deionized (D.I.) water. Stir until both solids have completely dissolved. Check pH is close to 3.5.

Note

Note 2. Preparation of saturated brine solution: Fill a container partially with D.I. water. Add a spatula full of sodium chloride (NaCl) and stir until dissolved. Repeat until excess NaCl begins to settle onto the bottom of the container.

[1]

Citation

C. S. Lancefield, N. J. Westwood (2015)
. The synthesis and analysis of advanced lignin model polymers. Green Chemistry.

10.1039/c5gc01334h LINK

[2]

Citation

Ciaran W. Lahive, Paul C. J. Kamer, C. S. Lancefield, Peter J. Deuss (2020)
. An introduction to model compounds of lignin linking motifs; synthesis and selection considerations for reactivity studies.
ChemSusChem.

10.1002/cssc.202000989 LINK

1.2 Licarin a (1.21 g , 3.71 mmol) was charged into a round-bottom flask and dissolved in methanol (45 mL) . 0.45 g 5 wt% Palladium on carbon (Pd-C) was added gently to the reaction mixture followed by 4.66 mL hydrochloric acid.

Safety information

Palladium on carbon can react violently with methanol causing a brief small flame.

The reaction was then stirred at room temperature under a hydrogen filled balloon for 44 hours. After which is was filtered and concentrated *in vacuo*.[3] Crude mixture was purified via flash chromatography to yield the final product as a light yellow oil (0.6785 g, 55.4%).

[3]

Citation

Fengxia Yue, Fachuang Lu, Matt Regner, Runcang Sun, John Ralph (2017)
. Lignin-Derived Thioacidolysis Dimers: Reevaluation, New Products, Authentication, and Quantification.
ChemSusChem.

10.1002/cssc.201700101 LINK

Purification

2 Flash chromatography was performed using a Teledyne Isco Combiflash® NextGen 300+. Collected fractions were determined using a UV detector with wavelengths set at 254 and 280 nm. Samples were prepared by dissolving the crude material in the smallest amount of compatible solvent. Silica gel (mesh size 70-230) was then added to adsorb the material. Excess solvent was vacuum evaporated and the sample was loaded into a RediSep® R_f 25 g sample cartridge (catalog # 69-3873-240).

2.1 Licarin a can be purified by recrystallization from methanol or by flash chromatography. Column used was a RediSep® Silver 80 g silica gel flash column (catalog # 69-2203-380). Solvent system was hexane (Solvent A) and ethyl acetate (Solvent B). Licarin a was separated from impurities using a ratio of 1:4 ethyl acetate:hexane.

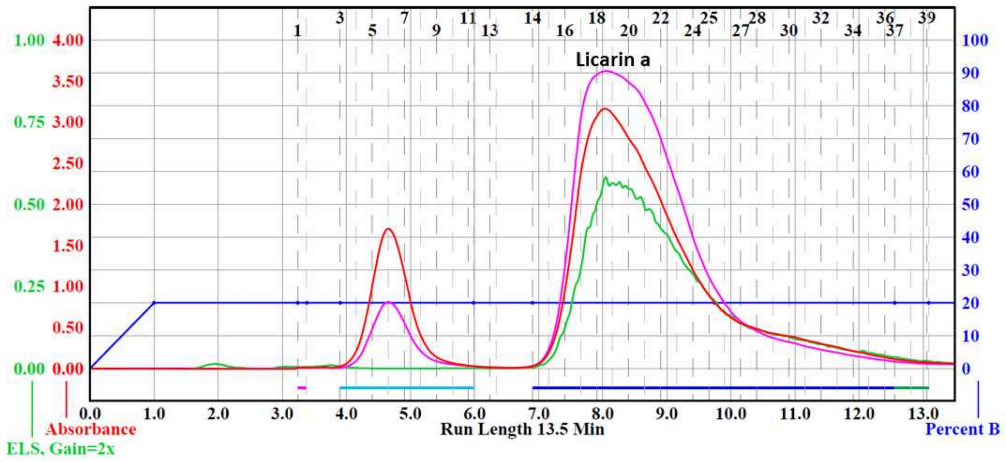

Figure 2. Run program from Combiflash® NextGen 300+ of licarin a separation.

2.2 2-(1-(4-hydroxy-3-methoxyphenyl)propan-2-yl)-6-methoxy-4-propylphenol was purified via flash chromatography. Column used was a RediSep® Silver 40 g silica gel flash column (catalog # 69-2203-340). Solvent system was hexane (Solvent A) and ethyl acetate (Solvent B). Material was separated from impurities using a ratio of 15% ethyl acetate and 75% hexane.

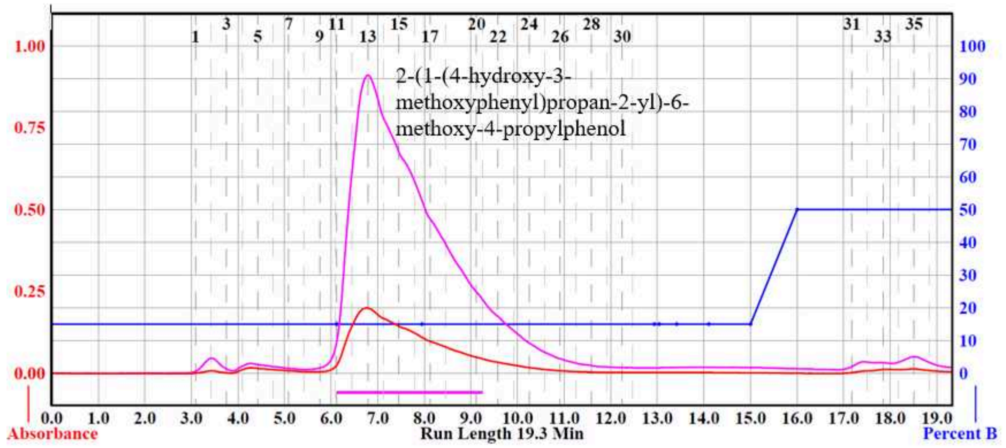

Figure 3. Run program from Combiflash® NextGen 300+ of 2-(1-(4-hydroxy-3-methoxyphenyl)propan-2-yl)-6-methoxy-4-propylphenol separation.

NMR Spectroscopy

3 Nuclear magnetic resonance (NMR) spectra are acquired in a suitable deuterated NMR solvent at 25°C on a Bruker AVANCE 400 MHz spectrometer equipped with a 5 mm BBO probe. Chemical shifts (δ) are reported in ppm. ^{1}H-NMR spectra are recorded with a relaxation delay of 1.0 s and an acquisition time of 4.09 s. The acquisition parameters for ^{13}C-NMR include a 90˚ pulse width, a relaxation delay of 1.0 s, and an acquisition time of 1.36 s. Tetramethylsilane is used as a reference.

3.1

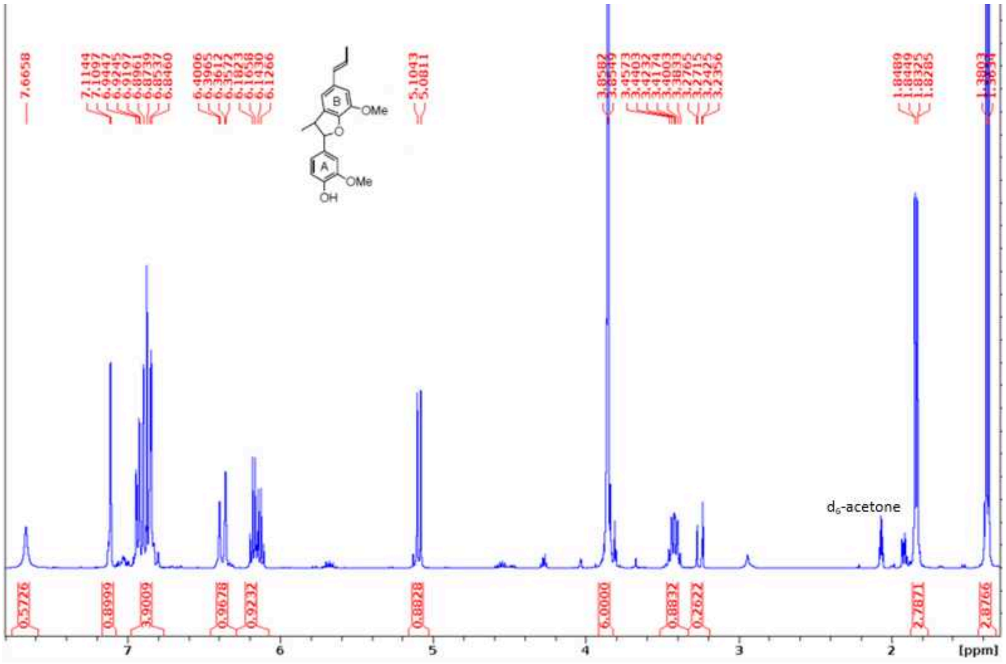

Figure 4. ^{1}H NMR spectrum of licarin a.

^{1}H NMR (400 MHz, d_6-acetone): *δ* 7.67 (s, 1H, ArOH), 7.11-6.84 (m, 5H, aromatic region), 6.40 (dd, *J* =14.2, 1.6 Hz, 1H, Bα), 6.18 (dq, *J* =9.1, 6.6 Hz, 1H, Bβ), 5.10 (d, J=9.3 Hz, 1H, Aα), 3.86 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.45 (dq, *J* =6.8, 2.3 Hz, 1H, Aβ), 1.84 (dd, *J* =4.9, 1.6 Hz, 3H, Bγ), 1.38 (d, *J*= 6.8 Hz, 3H, Aγ).

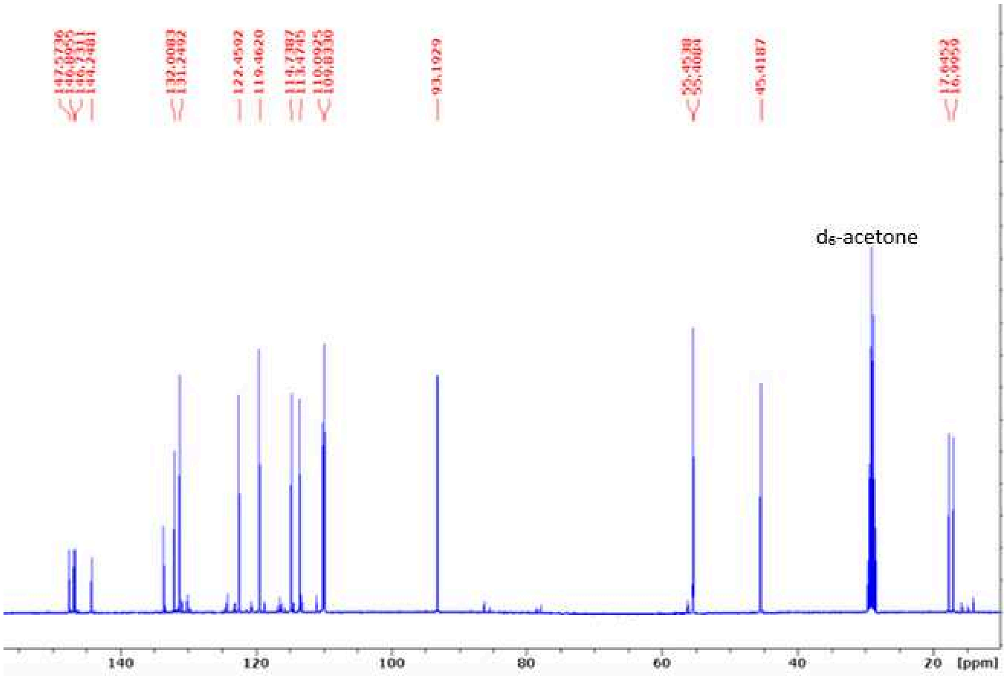

Figure 5. ^{1}H NMR spectrum of licarin a.

^{13}C NMR (100 MHz, d_6-acetone): δ 147.6 (A3), 146.9 (B3), 146.7 (A4), 144.2 (B4), 133.2 (B1), 132.0 (B5), 131.2 (A1), 130.9 (Bα), 122.4 (Bβ), 119.5 (A6), 114.7 (B6), 113.5 (A5), 110.1 (B2), 109.8 (A2), 93.2 (Aα), 55.5 (OMe), 55.4 (OMe), 45.4 (Aβ), 17.6 (Bγ), 16.9 (Aγ).

3.2

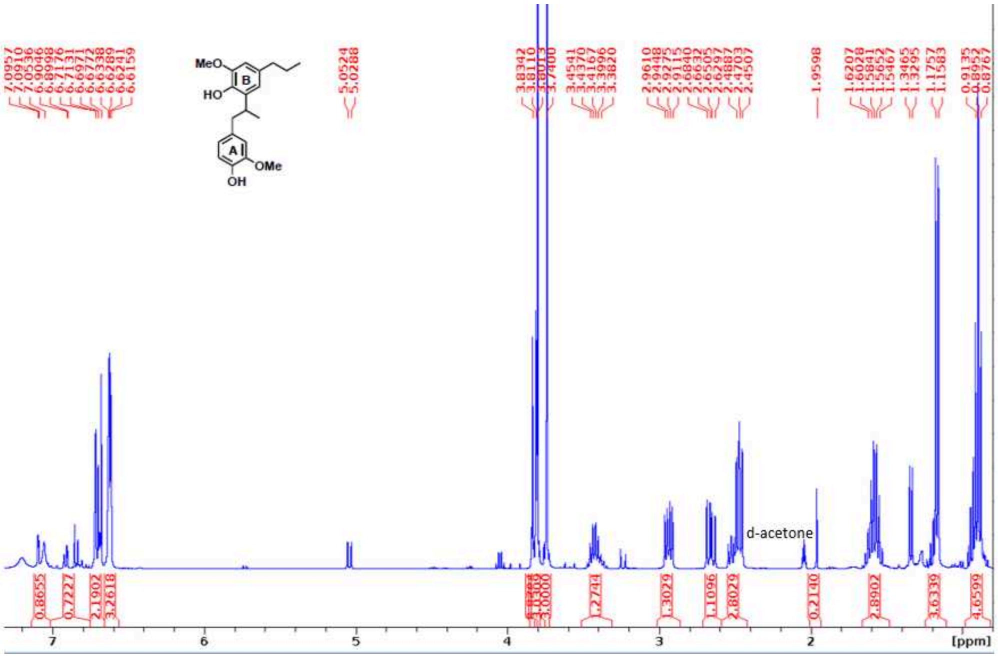

Figure 6. ^{1}H NMR spectrum of 2-(1-(4-hydroxy-3-methoxyphenyl)propan-2-yl)-6-methoxy-4-propylphenol.

^{1}H NMR (400 MHz, d_6-acetone): δ 6.72 (d, J = 1.8 Hz, 1H, A2), 6.69 (d, J = 7.9 Hz, 1H, A5), 6.63 (d, J = 1.9 Hz, 1H, B2), 6.62 (dd, J = 6.8, 1.2 Hz, 1H, A6), 6.61 (d, J = 1.2 Hz, 1H, B6), 3.81 (s, 3H, B3-OMe), 3.74 (s, 3H, A3-OMe), 3.45 (sex, J = 6.8 Hz, 1H, Aβ), 2.96 (dd, J = 6.6 Hz, 1H, Aα1), 2.68 (dd, J = 8.3, 5.1 Hz, 1H, Aα2), 2.48 (t, J = 7.4 Hz, 2H, Bα), 1.62 (sex, J = 7.2 Hz, 2H, Bβ), 1.17 (d, J = 6.9 Hz, 3H, Aγ), 0.91 (t, J = 7.3 Hz, 3H, Bγ).

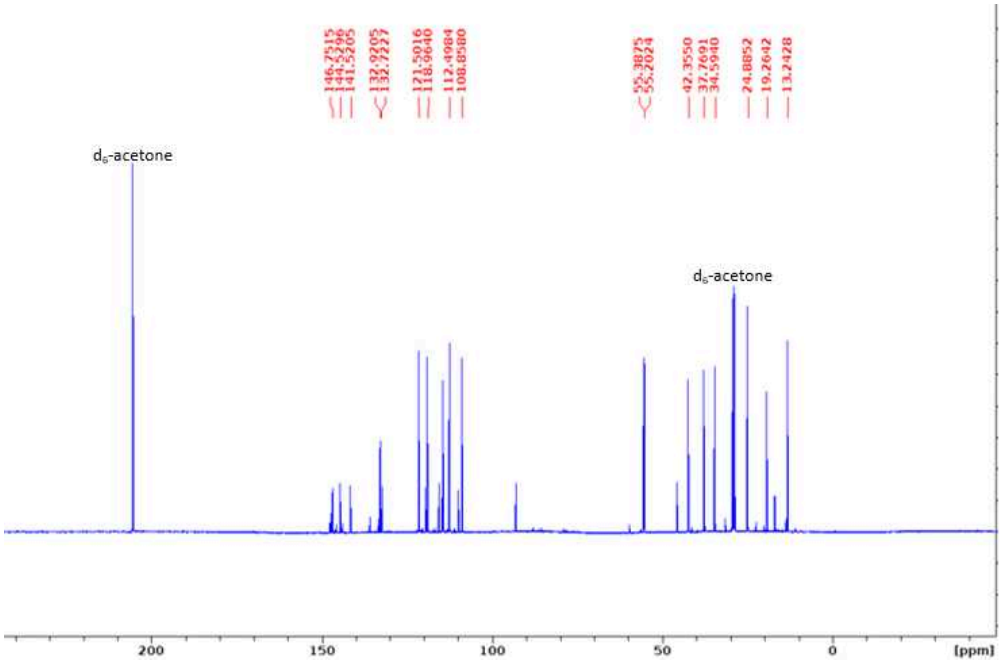

Figure 7. ^{13}C NMR spectrum of 2-(1-(4-hydroxy-3-methoxyphenyl)propan-2-yl)-6-methoxy-4-propylphenol.

^{13}C NMR (100 MHz, d_6-acetone): δ 146.75 (A3), 146.31 (B3), 144.53 (A4), 141.52 (B4), 132.92 (B1), 132.72 (A1), 132.04 (B5), 121.50 (A6), 118.96 (B6), 114.22 (A5), 112.50 (A2), 108.86 (B2), 55.39 (B-OMe), 55.20 (A-OMe), 42.36 (Aα), 37.77 (Bα), 34.59 (Aβ), 24.89 (Bβ), 19.26 (Aγ), 13.24 (Bγ).

[4]

Citation

S. A. Ralph, L. L. Landucci, J. Ralph (2009). NMR Database of Lignin and Cell Wall Model Com

https://www.glbrc.org/databases_and_software/nmrdatabase/NMR_DataBase_2009_Cc
LINK

Citations

Step 1.1

Ciaran W. Lahive, Paul C. J. Kamer, C. S. Lancefield, Peter J. Deuss. An introduction to model compounds of lignin linking motifs; synthesis and selection considerations for reactivity studies
10.1002/cssc.202000989

Step 1.1

C. S. Lancefield, N. J. Westwood. The synthesis and analysis of advanced lignin model polymers
10.1039/c5gc01334h

Step 1.2

Fengxia Yue, Fachuang Lu, Matt Regner, Runcang Sun, John Ralph. Lignin-Derived Thioacidolysis Dimers: Reevaluation, New Products, Authentication, and Quantification
10.1002/cssc.201700101

Step 3.2

S. A. Ralph, L. L. Landucci, J. Ralph. NMR Database of Lignin and Cell Wall Model Compounds
https://www.glbrc.org/databases_and_software/nmrdatabase/NMR_DataBase_2009_Complete.pdf