

A Convenient Synthesis of an Anti-Helicobacter Pylori Agent, Dehydrodiconiferyl Alcohol

Kun Hu and Jin-Hyun Jeong

College of Pharmacy, Kyung Hee University, Seoul 130-701, Korea

(Received May 15, 2006)

Potential anti-Helicobacter pylori agent dehydrodiconiferyl alcohol was synthesized in 44% overall yield, starting from vanillin which could be commercially available. Carbon extension of vanillin followed by the Horner-Wadsworth-Emmons reaction, a biomolecular radical coupling reaction and DIBAL-H reduction gave dehydrodiconiferyl alcohol.

Key words: Anti-Helicobacter pylori agent, Dehydrodiconiferyl alcohol, Vanillin, Horner-Wadsworth-Emmons reaction, Radical coupling reaction

INTRODUCTION

Lignan compound have already been reported to have the anti-Helicobacter pylori activity (Ochi *et al.*, 2005). Dehydrodiconiferyl alcohol (1), is one of the neolignan compound, which is believed to be precursor of lignin (Freudenberg, 1965; Lewis and Yamamoto, 1990), and its derivatives have been reported to have as anti-oxidative (Takara *et al.*, 2000) and cytokinin-like (Lynn *et al.*, 1987; Binns, 1987) biological activities, but few literature reported the anti-Helicobacter pylori activity of it. So we focus on studying the anti-Helicobacter pylori activity of dehydrodiconiferyl alcohol and its derivatives. Unfortunately, there have been few efficient synthesis methods for dehydrodiconiferyl alcohol reported (1). Most of the synthesis methods imitate its biosynthesis, using an oxidation coupling reaction of coniferyl alcohol with peroxidase as the catalyst (Haikarainen *et al.*, 2001; Syrjanen and Brunow, 1998, 2001; Fernandes *et al.*, 1999).

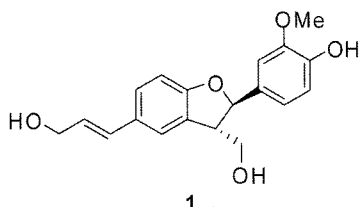
Obviously, this method is expensive, and the reaction conditions are rigorous. Other methods either require a lengthy work-up or lack convergent property (Ezio Bolzacchini *et al.*, 1998). Therefore, efficient, commercial and convergent synthesis approach for dehydrodiconiferyl alcohol (1) is needed.

MATERIALS AND METHODS

¹H-NMR and ¹³C-NMR were recorded in the solvent indicated at 200 and 50MHz, respectively. Chemical shifts are expressed in parts per million downfield from TMS. Flash chromatography was performed with 40-63 μm silica gel. TLC was performed on silica gel 60 plates with an F₂₅₄ indicator and visualized under UV light or developed by immersion in a solution of 20% phosphomolybdic acid in ethanol or in a solution of 1.0% KMnO₄.

3-(4-Hydroxy-3-methoxy-phenyl)-acrylic acid ethyl ester (3)

Sodium hydride (60% dispersion in mineral oil, 44 mg, 1.1 mmole) was placed in 5 mL dry THF. The slurry was cooled to -20°C and triethyl phosphonoacetate (246.6 mg, 1.1 mmole) was added dropwise with stirring. After the addition, the solution was stirred at room temperature for 1 h until gas evolution had ceased. The solution was recooled to -20°C, and to this yellow, was added dropwise THF solution of vanillin (152 mg, solution 1 mmole). During the addition, a gummy precipitate appeared. The solution was heated to the room temperature in 10 minutes, and stirred at this temperature for 1 hours and reflux for 30



Correspondence to: Jin-Hyun Jeong, College of Pharmacy, Kyung Hee University, #1 Hoegi-Dong, Dongdaemun-Gu, Seoul 130-701, Korea
Tel: 82-2-961-0368, Fax: 82-2-961-0357
E-mail: jeongjh@khu.ac.kr

minutes. After cooling, a large excess of water was added and the product extracted with ethyl acetate. The ethyl acetate, after being dried over magnesium sulfate, was removed to give the crude product. The residue was purified by flash column chromatography (eluant, *n*-hexane/ethyl acetate = 5:1 v/v) to afford 217.8 mg (98%) of the title compound as a yellow oil: Rf=0.5 (*n*-hexane/ethyl acetate = 7:3 v/v); ¹H-NMR (200MHz, CDCl₃) δ1.30 (3H, t, *J* = 4.4 Hz), 3.83 (3H, s), 4.19 (2H, q, *J* = 4.4 Hz), 6.39 (1H, d, *J* = 7.7 Hz), 6.79 (1H, d, *J* = 8.8 Hz), 6.99 (1H, d, *J* = 8.8 Hz), 7.16 (1H, s), 7.64 (1H, d, 7.7Hz), ¹³C-NMR (50 MHz, CDCl₃) δ14.2, 56.1, 61.4, 111.9, 116.2, 116.8, 120.1, 128.8, 144.9, 145.2, 151.3, 166.5.

5-(2-Ethoxycarbonyl-vinyl)-2-(4-hydroxy-3-methoxyphenyl)-2,3-dihydro-benzofuran-3-carboxylic acid ethyl ester (4)

Silver (I) oxide (56 mg, 0.24 mmol) was added to a dry CH₂Cl₂ solution (5 mL) of compound **3** (107 mg, 0.48 mmol). The reaction mixture was stirred until complete disappearance of compound **3**, and then filtered through a bed of celite, extracted with ethyl acetate and washed with saturated aqueous NaCl, dried over magnesium sulfate and evaporated to dryness. The residue was then purified by flash column chromatography (eluant, *n*-hexane/ethyl acetate = 5:1 v/v) to afford 53 mg (50%) of the title compound as a yellow oil: Rf=0.54 (eluant, *n*-hexane/ethyl acetate = 5:3 v/v); ¹H-NMR (200 MHz, CDCl₃) δ1.30 (3H, t, *J* = 4.2 Hz), 1.32 (3H, t, *J* = 4.1 Hz), 3.72(3H, s), 4.10 (2H, q, 4.2 Hz), 4.17 (2H, q, 4.1 Hz), 4.49 (1H, d, 3.8 Hz), 5.96 (1H, 3.8 Hz), 6.39 (1H, d, *J* = 7.8 Hz), 6.53 (1H, s), 6.55 (1H, d, *J* = 8.6 Hz), 6.58 (1H, d, *J* = 8.6Hz), 6.67 (1H, d, *J* = 8.4 Hz), 7.01 (1H, d, *J* = 8.4 Hz), 7.05 (1H, s), 7.64 (1H, d, 7.8 Hz), ¹³C-NMR (50 MHz, CDCl₃) δ14.1, 14.2, 56.1, 61.4, 61.6, 66.2, 87.7, 112.5, 114.7, 116.2, 117.1, 120.8, 124.4, 125.8, 127.2, 127.9, 134.2, 144.6, 145.2, 151.6, 166.5, 173.7.

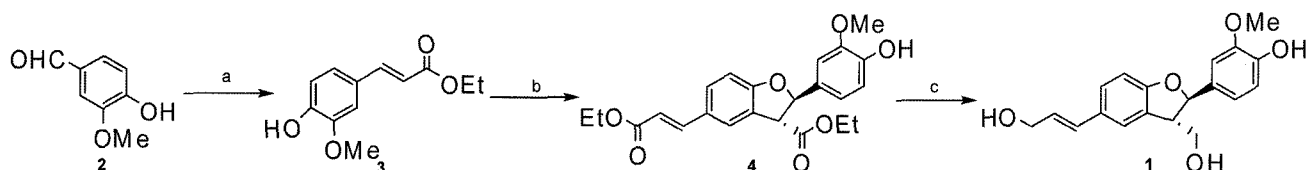
4-[3-Hydroxymethyl-5-(3-hydroxy-propenyl)-2,3-dihydro-benzofuran-2-yl]-2-methoxy-phenol (5)

Compound **4** (100 mg, 0.23 mmol) in toluene (5 mL, freshly distilled), under nitrogen, was cooled in an ice-water bath, and diisobutylaluminium hydride (1M hexane solution) was slowly added *via* syringe. After the addition,

stirring was continued for ca. 1 h. The mixture was then carefully quenched with 5 mL ethanol. The solvents were partially removed *in vacuo* at 40°C. Water 20 mL was added, and the aqueous layer, containing a gelatinous precipitate of aluminium salts, was extensively extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo* at 35°C. The residue was then purified by flash column chromatography (eluent, *n*-hexane/ethyl acetate = 1:10) to afford 68 mg (90%) of the title compound as a colorless oil: Rf = 0.25 (eluant, *n*-hexane/ethyl acetate = 3:7 v/v); ¹H-NMR (200 MHz, CDCl₃) δ1.97 (2H, br), 3.56 (1H, ddd, *J* = 6.8, 6.3, 5.5 Hz), 3.78 (3H,s), 3.81 (1H, dd, *J* = 11.9, 6.3 Hz), 3.88 (3H, s), 3.89 (1H, dd, *J* = 11.9, 5.5 Hz), 4.2 (2H, dt, *J* = 5.2, 1.3 Hz), 5.50 (1H, d, *J* = 6.8 Hz), 6.14 (1H, dt, *J* = 16.1, 5.2 Hz), 6.18 (1H, d, *J* = 16.1 Hz), 6.46 (1H, d, *J* = 8.3 Hz), 6.50 (1H, dd, *J* = 8.3, 2.0 Hz), 6.79 (1H, s), 6.82 (1H, s), 6.84 (1H, d, *J* = 2.0), ¹³C-NMR (CDCl₃) δ53.66, 56.13, 60.56, 63.96, 64.12, 88.38, 108.90, 110.62, 114.48, 114.94, 119.56, 126.57, 130.88, 128.26, 131.06, 131.47, 133.02, 145.86, 146.83, 148.48.

RESULTS AND DISCUSSION

Our strategy used cheap and easily available vanillin (**2**) as a starting material, and used the Horner-Wadsworth-Emmons reaction to produce the important intermediate ethyl ferulate displacing the esterification of ferulic acid (Harri Setala, 1998; Petteri Rummakko *et al.*, 1999; Marco Orlandi *et al.*, 2001; Strehlke and Kessler, 1979; Chai-Lin Kao and Ji-Wang Chern, 2001, 2002). This modification has many merits such as a very high yield, very diversified and the *cis-trans* isomerism of the unsaturated ester can be easily controlled by controlling the reaction conditions and reaction reagents (Kaori Ando, 1997), although there is little influence on the *cis-trans* isomerism of the side chain of the product after the oxidation coupling reaction (John Ralph and Yinsheng Zhang, 1998). The reaction mixture is easy to work-up because the byproduct is soluble in water. For the oxidation coupling reaction, silver (I) oxide was used as the oxidant instead of the expensive and condition-dependent peroxidase (Quideau and Ralph, 1994; Lemiere *et al.*, 1995). The DIBAL-H reduction was



Scheme 1. Synthetic scheme of dehydrodiconiferyl alcohol. Reagents and conditions: (a) Triethyl phosphonoacetate, NaH, THF, -20°C-reflux, 2.5 h; (b) Ag₂O, CH₂Cl₂, r.t., 4 h; (c) DIBAL-H, toluene, 0°C, 1 h.

performed on the modified method for reducing ethyl ferulate to coniferyl alcohol, which was reported by Stephane Quideau and John Ralph in 1992, to give the final product in very high yield (Stephane Quideau and John Ralph, 1992).

In summary, Our investigation provided a practical approach toward synthesizing dehydrodiconiferyl alcohol (1). Its analogs can also be simply synthesized either by the functionalization at the carbonyl of vanillin (4) or by using a variety of vanillin (4) analogs as the starting material. Using this strategy, the synthesis of other neolignan and lignan derivatives is currently under active investigation in our laboratory.

ACKNOWLEDGEMENT

Author is supported from the Post-BK21 project.

REFERENCES

- Binns, A. N., Chen, R. H., Wood, H. N., and Lynn, D. G., Cell division promoting activity of naturally occurring dehydrodiconiferyl glucosides: Do cell wall components control cell division? *Proc. Natl. Acad. Sci. U.S.A.*, **84**, 980-984 (1987).
- Chai-Lin Kao and Ji-Wang Chern, A convenient synthesis of naturally occurring benzofuran aianthoidol. *Tetrahedron Lett.*, **42**, 1111-1113 (2001).
- Chai-Lin Kao and Ji-Wang Chern, A novel strategy for the synthesis of benzofuran skeleton neolignans: Application to aianthoidol, XH-14, and obovaten. *J. Org. Chem.*, **67**, 6772-6787 (2002).
- Ezio Bolzacchini, Gosta Brunow, Simore Meinardi, Marco Orlandi, Bruno Rindone, Petteri Rummakko, and Harri Setälä, Enantioselective synthesis of a benzofuranic neolignan by oxidation coupling. *Tetrahedron Lett.*, **39**, 3291-3294 (1998).
- Fernandes, Eduarda G. R., Pinto, Madalena M. M., Silver, Artur M. S., Cavaleiro, Jose A. S., and Gottlieb, Otto R., Synthesis and structural Elucidation of Xanthonolignoids: trans-(±)-Kielcorin B and trans-(±)-Isokielcorin B., *Heterocycles*, **51**, 821-828 (1999).
- Freudenberg, K., Lignin: Its constitution and formation from *p*-hydroxycinnamyl alcohols. *Science*, **148**, 595-600 (1965).
- Haikarainen, A., Sipila, J., Pietikainen, P., Pajunen, A., and Mutikainen, I., Salen complexes with bulky substituents as useful tools for biomimetic phenol oxidation research. *Bioorg. Med. Chem.*, **9**, 1633-1638 (2001).
- John Ralph; Yinsheng Zhang. A new synthesis of (Z)-coniferyl alcohol, and characterization of its derived synthetic lignin. *Tetrahedron*, **54**, 1349-1354 (1998).
- Kaori Ando, Highly Selective Synthesis of Z-Unsaturated Esters by Using New Horner-Emmons Reagents, Ethyl (Diarylphosphono) acetates. *J. Org. Chem.*, **62**, 1934-1939 (1997).
- Lemiere, G., Gao, M., De Groot, A., Domisse, R., Lepoivre, J., and Pieters, B., *Perkin Trans.1*, 3', 4-Di-O-methylcedrusin: synthesis, resolution and absolute configuration. *J. Chem. Soc.*, 1775 (1995).
- Lewis, G. N. and Yamamoto, E. Annu, Lignin: occurrence, biogenesis and biodegradation. *Rev. Plant Mol. Biol.*, **41**, 455-496 (1990).
- Lynn, A. N., Chen, R. H., Manning, K. S., and Wood, H. N., The structural characterization of endogenous factors from *Vinca rosea* crown gall tumors that promote cell division of tobacco cells. *Proc. Natl. Acad. Sci. U.S.A.*, **84**, 615-619 (1987).
- Marco Orlandi, Bruno Rindone, Giorgio Molteni, Petteri Rummakko, and Gosta Brunow, Asymmetric biomimetic oxidations of phenols: the mechanism of the diastereo- and enantioselective synthesis of dehydrodiconiferyl ferulate (DDF) and dehydrodiconiferyl alcohol (DDA). *Tetrahedron*, **57**, 371-378 (2001).
- Ochi, T., Takaishi, Y., Shibata, H., Higuti, T., and Kataoka, M., Chemical constituents of *Capsicum annuum* L var. *angulosum*, and anti *Helicobacter pylori* activity, *Natural Medicines*, **59**, 76-84 (2005).
- Petteri Rummakko, Gosta Brunow, Marco Orlandi, and Bruno Rindone, Asymmetric biomimetic oxidations of phenols: enantioselective synthesis of (+)- and (-)-Dehydrodiconiferyl alcohol. *Synlett*, **3**, 333-335 (1999).
- Quideau, S. and Ralph, J., A biomimetic route to lignin model compounds via Silver (I) oxide oxidation. *Holzforshung*, **48**, 12 (1994).
- Stephane Quideau and John Ralph, Facile large-scale synthesis of coniferyl, sinapyl, and *p*-coumaryl alcohol. *J. Agric. Food Chem.*, **40**, 1108-1110 (1992).
- Strehlke, P. and Kessler, H. J., *European J. of Med. Chem.*, **14**, 238-242 (1979).
- Syjanen, K. and Brunow, G., Oxidation cross coupling of *p*-hydroxycinnamic alcohols with dimeric arylglycerol β-aryl ether lignin model compounds. The effect of oxidation potentials. *J. Chem. Soc. Perkin Trans.*, **1**, **20**, 3425-3430 (1998).
- Syrjanen, K. and Brunow, G., Regioselectivity in oxidative cross-coupling of phenols. Application to the synthesis of dimeric neolignans. *Tetrahedron*, **57**, 365-370 (2001).
- Takara, K., Kjnjo, A., Matsui, D., Wada, K., Nakasone, Y., and Yogi, S., Antioxidative phenolic compounds from non-sugar fraction in *kokuto*, non-centrifugal cane sugar. *Nippon Nogeikagaku Kaishi (in Japanese)*, **74**, 885-890 (2000).