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NOTE

Shingo Kawai · Kyoko Okita · Kazuhiro Sugishita
Ai Tanaka · Hideo Ohashi

Simple method for synthesizing phenolic β-*O*-4 dilignols

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Abstract A modified synthetic method for phenolic β-*O*-4 lignin substructure model dimers was developed involving protection of the phenolic hydroxyl group of acetophenons with benzoyl chloride, bromination with 4-dimethylaminopyridiniumbromide perbromide, condensation with phenols in the presence of 18-crown-6-ether, condensation with paraformaldehyde, reduction with $NaBH_4$, and debenzoylation. This method results in shorter reaction times and increasing yields without the application of strict anhydrous and drastic conditions or chloric solvents. This alternative route could be applied to the β-*O*-4 dilignol syntheses of four combinations of guaiacyl and syringyl derivatives.

Key words β-*O*-4 Dilignols · Chemical synthesis · Chloric solvents · Anhydrous condition · Mild condition

Introduction

The use of various dilignols (lignin substructure model compounds) makes possible a detailed study of the chemical and biochemical reactivities of the lignin macromolecule. Because it is a major interphenylpropane linkage in lignin, it is essential to investigate the β-*O*-4 substructure using β-*O*-4 dilignols.

A number of synthetic methods for the production of β-*O*-4 dilignols have been reported.[1–14] Most of them suffer from different reactivities of the starting materials, undesirable side reactions, or difficulty handling reagents.

The present study focused first on environmental considerations. Use of the chloric solvents CCl_4, $CHCl_3$, and CH_2Cl_2 has been regulated because of their harmful effects on human health and the environment. Thus, alternative or modified reagents and solvents must soon be developed. Second, we wished to avoid complicated reaction conditions. The convergent synthesis of β-*O*-4 dilignol designed by Nakatsubo et al.[6,11] is an excellent, elegant method but one that requires a strict anhydrous condition for the condensation reaction with lithium diisopropyl amide. Finally, we considered the reactivities between guaiacyl and syringyl nuclei. The reported procedures to date have mainly mentioned synthesis of guaiacyl-type of compounds, but synthesis of a syringyl-type compound has not received as much attention except for the method of Nakatsubo.[11]

We report a simple method to synthesize four β-*O*-4 dilignols (**1**)–(**4**) from acetophenone derivatives. It has resulted in a good yield.

Experiment

Analytical and preparative thin-layer chromatography (TLC) utilized silica gel (Merck Kieselgel 60 F_{254}; solvent system: ethyl acetate-*n*-hexane). Column chromatography employed Fuji silysia BW-200. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained with a Varian FT-NMR Unity Inova 400 using tetramethylsilane as an internal standard. Electron ionization–mass spectrometry (EI-MS) analyses were performed with a Simadzu GCMS-QP 5000 gas chromatography mass spectrometer (70 eV). The working-up of the reactions was done when starting materials disappeared or formation of a considerable amount of by-products was detected by checking the TLC.

S. Kawai (✉) · K. Okita[1] · K. Sugishita[2] · A. Tanaka[3] · H. Ohashi
Department of Applied Bioorganic Chemistry, Faculty of Agriculture, Gifu University, Yanagido, Gifu 501-1193, Japan
Tel. +81-58-293-2920; Fax +81-58-293-2915
e-mail: skawai@cc.gifu-u.ac.jp

Present address:
[1]Yutaka Foods Co., Taketoyo, Aichi 470-2395, Japan
[2]YMC Co., Komatsu, Ishikawa 923-8557, Japan
[3]Kato Chemicals Co., Taketoyo, Aichi 470-2409, Japan
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The reagents and solvents were used without further purification.

4′-Benzyloxy-3′,5′-dimethoxyacetophenone (**6**) (step **a**)

A solution of 3′,5′-dimethoxy-4′-hydroxyacetophenone (**5**) (396.4 mg, 2 mmol) (acetosyringone 99%; Aldrich) in pyridine (3 ml) was cooled at 0°C with stirring; benzoyl chloride (277 µl, 2.4 mmol) was added under nitrogen atmosphere (white precipitate was formed). The resulting solution was stirred at 0°C for 10 min. The reaction mixture was partitioned between ethyl acetate (50 ml) and 1 N HCl (30 ml). The organic layer was washed successively with 1 N HCl (20 ml, twice), 1 N NaOH (20 ml, twice), and saturated brine (30 ml, twice). It was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield a crude 4′-benzoyloxy-3′,5′-dimethoxyacetophenone (**6**) (790 mg). The product was used for the next step without further purification.

1-(4-Benzoyloxy-3,5-dimethoxyphenyl)-2-bromoethanone (**7**) (step **b**)

To a solution of crude compound **6** (790 mg) in ethyl acetate (3 ml), 4-dimethylaminopyridiniumbromide perbromide (1.1 g, 3.0 mmol) (Tokyo Chemical Industry) was added under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 30 min. The reaction mixture was partitioned between ethyl acetate (50 ml) and water (30 ml). The organic layer was washed successively with water (20 ml, twice) and saturated brine (30 ml, twice). It was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was recrystallized from a mixture of acetone and *n*-hexane to give white crystals of 1-(4-benzoyloxy-3,5-dimethoxyphenyl)-2-bromoethanone (**7**) (610.0 mg, yield 80.4% from acetosyringone), mp 165°–167°C. [*Note*: Compound **7** and its analogue were also purified by column chromatography with ethyl acetate-*n*-hexane, 1:3.]

1-(4-Benzoyloxy-3,5-dimethoxyphenyl)-2-(2,6-dimethoxyphenoxy)ethanone (**8**) (step **c**)

To a solution of compound **7** (610.0 mg, 1.61 mmol) in toluene (3 ml), pyrogallol-1,3-dimethyl ether (372.3 mg, 2.42 mmol) (2,6-dimethoxyphenol, Nakarai Tesuqe), 18-crown-6-ether (639.7 mg, 2.42 mmol), and KOH (159.7 mg, 2.42 mmol; 85% KOH was powdered with mortar and pestle) was added under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 35 min. The reaction mixture was partitioned between ethyl acetate (50 ml) and water (30 ml). The organic layer was washed with saturated brine (30 ml, twice), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent was ethyl acetate-*n*-hexane, 1/2) to give a white crystal of 1-(4-benzoyloxy-3,5-dimethoxyphenyl)-2-(2,6-dimethoxyphenoxy)ethanone (**8**) (677.3 mg, yield 93.1%), mp 136°–138°C. [*Note*: If the reaction is not completed, add 0.5 equivalent of phenols to the reaction mixture. Compound **8** and its analogue were also purified by recrystallization from ethyl acetate and *n*-hexane.]

1-(4-Benzoyloxy-3,5-dimethoxyphenyl)-2-(2,6-dimethoxyphenoxy)-3-hydroxypropane (**9**) (step **d**)

To a solution of compound **8** (677.3 mg, 1.50 mmol) in dimethylsulfoxide (2.5 ml), paraformaldehyde (56.8 mg, 1.80 mmol; 95%) and K_2CO_3 (62.2 mg, 0.45 mmol) were added under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 85 min. The reaction mixture was partitioned between ethyl acetate (50 ml) and water (30 ml). The organic layer was washed with saturated brine (30 ml), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent was ethyl acetate-*n*-hexane, 1:1) to give 1-(4-benzoyloxy-3,5-dimethoxyphenyl)-2-(2,6-dimethoxyphenoxy)-3-hydroxypropane (**9**) (632.2 mg, yield 87.5%). [*Note*: If the reaction is not completed, add 0.5 equivalent of paraformaldehyde to the reaction mixture.]

1-(4-Benzoyloxy-3,5-dimethoxyphenyl)-1,3-dihydroxy-2-(2,6-dimethoxyphenoxy)propane (**10**) (step **e**)

To a solution of compound **9** (632.2 mg, 1.31 mmol) in methanol (1.5 ml) and tetrahydrofuran (2 ml), sodium borohydride (99.1 mg, 2.62 mmol) was added at 0°C. The resulting solution was stirred at 0°C for 5 min. The reaction mixture was partitioned between ethyl acetate (50 ml) and water (30 ml). The organic layer was washed with saturated brine (30 ml, twice), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a crude mixture of 1-(4-benzoyloxy-3,5-dimethoxyphenyl)-1,3-dihydroxy-2-(2-methoxyphenoxy)propane (**10**) (683 mg). The product was used for the next step without further purification.

1,3-Dihydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)-2-(2,6-dimethoxyphenoxy)propane (**1**) (step **f**)

To a solution of crude compound **10** (683 mg) in benzene (2 ml), *n*-butylamine (1.3 ml, 13.1 mmol) was added under nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 72 h. The reaction mixture was partitioned between ethyl acetate (50 ml) and 1 N HCl (30 ml). The organic layer was washed with saturated brine (30 ml, twice), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (eluent was ethyl acetate-*n*-hexane, 3:1) to give *erythro* and *threo* (2:5) mixtures of 1,3-dihydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)-2-(2,6-dimethoxyphenoxy)propane (**1**) (494.0 mg, yield 99.1% from compound **9**).

MS *m/z* (%): 380 (M^+, 1.1), 332 (8), 181 (18), 180 (100), 167 (15), 154 (63), 153 (11), 151 (26), 149 (12), 139 (32), 123 (12), 111 (12), 110 (12), 107 (12).

Erythro and *threo* isomers of 1,3-dihydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)-2-(2,6-dimethoxyphenoxy)propane (**1**)

The hydroxyl groups of C_1 and C_3 position of compound **10** were protected with 2,2-dimethoxypropane[15] before deprotection of benzoyl group. The *erythro* and *threo* isomers of acetonide compounds **11** could be separated from each other by column chromatography (eluent was ethyl acetate-*n*-hexane, 1:1). The deprotection of the benzoyl group and acetonide of the isomers, respectively, gave both isomers of **1**.

^{1}H-NMR δ (ppm, C^2HCl_3) of *erythro* isomer: 3.40–3.55 (1H, m, C_3H), 3.87 (6H, s, OMe), 3.89 (6H, s, OMe), 3.85–4.00 (1H, m, C_3H), 4.10–4.20 (1H, m, C_2H), 5.00 (1H, d, J = 3.7, C_1H), 6.58 (2H, s, $C_{2'\ \&\ 6'}$H), 6.66 (2H, d, J = 8.4, $C_{3''\ \&\ 5''}$H), 7.10 (1H, t, J = 8.4, $C_{4''}$H). *Threo* isomer: 3.25–3.40 (1H, m, C_3H), 3.60 (1H, dd, J = 2.9, 12, C_3H), 3.89 (6H, s, OMe), 3.91 (6H, s, OMe), 4.10–4.20 (1H, m, C_2H), 5.27 (1H, d, J = 8.8, C_1H), 6.64 (2H, d, J = 8.4, $C_{3''\ \&\ 5''}$H), 6.72 (2H, s, $C_{2'\ \&\ 6'}$H), 7.07 (1H, t, J = 8.4, $C_{4''}$H). ^{13}C-NMR δ (ppm, C^2HCl_3) of *erythro* isomer: 56.1 (2C, OMe), 56.3 (2C, OMe), 60.4 (C_3), 74.3 (C_1), 89.0 (C_2), 103.9 (2C, $C_{3''\ \&\ 5''}$), 105.2 (2C, $C_{2'\ \&\ 6'}$), 124.5 ($C_{4'}$), 131.0 ($C_{4''}$), 134.3 ($C_{1''}$), 135.2 ($C_{1'}$), 146.9 (2C, $C_{2''\ \&\ 6''}$), 153.2 (2C, $C_{3'\ \&\ 5'}$). *Threo* isomer: 56.1 (2C, OMe), 56.3 (2C, OMe), 60.5 (C_3), 72.6 (C_1), 87.0 (C_2), 102.4 (2C, $C_{3''\ \&\ 5''}$), 105.2 (2C, $C_{2'\ \&\ 6'}$), 124.5 ($C_{4''}$), 130.3 ($C_{4'}$), 133.8 ($C_{1''}$), 134.9 ($C_{1'}$), 147.0 (2C, $C_{2''\ \&\ 6''}$), 153.5 (2C, $C_{3'\ \&\ 5'}$).

Results and discussion

The synthetic route of β-*O*-4 dilignols is indicated in Fig. 1. This route is based on the method proposed by Adler and Eriksoo.[2]

We employed benzoyl chloride for the protection of phenolic hydroxyl groups of acetophenones (step **a**). In addition to the benzyl analogue being partially cleaved by HBr formed during bromination reactions (e.g., step **b**), bromo-substitution into the syringyl nucleus occurred owing to the benzyl group in the case of an acetosyringone derivative (data not shown). The electron density on the aromatic ring of the syringyl group is higher than that of the guaiacyl group due to the electron donation of the alkoxyl groups. We have already reported on the different reactivities between the guaiacyl and syringyl nuclei of β-*O*-4 dilignols by intact culture[16] and on lignin peroxidase[17] of *Trametes Coriolus versicolor* and of cinnamyl aldehydes by thioacidolysis.[18] The acetyl group results in a low yield for bromination of the acetovanillone derivative (data not shown). Such problems did not arise when the benzoyl group was used as the protecting group.

For the bromination reagent, we used 4-dimethylaminopyridiniumbromide perbromide in ethyl acetate instead of methylene chloride[13] (step **b**). The reaction resulted in a good yield without using a chloric solvent at ambient temperature.

The substitution of 2,6-dimethoxyphenol (step **c**) was performed with potassium hydroxide and a phase-transfer catalyst, 18-crown-6-ether, in toluene. When the replacement reaction is done with potassium carbonate in DMF, in some cases a crystalline product is formed during the procedure, making it difficult to extract with diethyl ether. In the

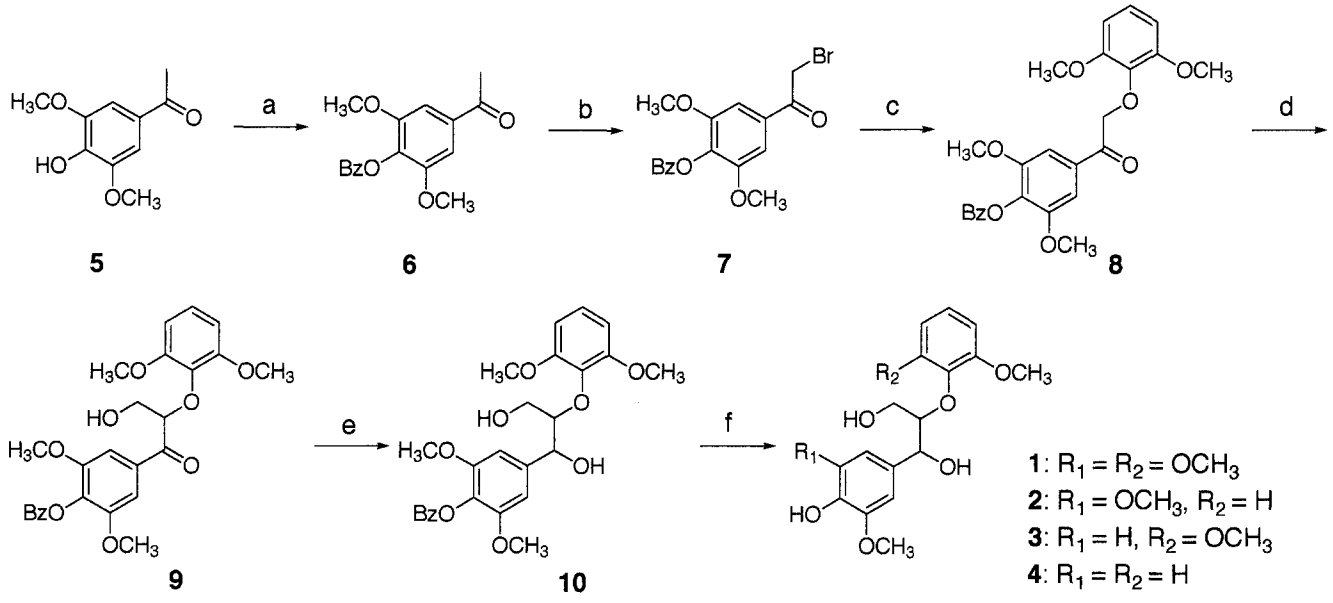

Fig. 1. Synthetic route of 1,3-dihydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)-2-(2,6-dimethoxyphenoxy)propane (**1**) and the structure of β-*O*-4 dilignols (**1**)–(**4**). Bz, benzoyl (C_6H_5CO-). r.t., room temperature. [a] C_6H_5COCl/pyridine/0°C. [b] 4-dimethylaminopyridiniumbromide perbromide/EtOAc/r.t. [c] 2,6-dimethoxyphenol/KOH/18-crown-6-ether/toluene/r.t. [d] -$(CH_2O)_n$-/K_2CO_3/DMSO/r.t. [e] $NaBH_4$/MeOH/0°C. [f] *n*-butylamine/benzene/r.t.

Table 1. Yields of reaction steps **a–f** and overall yields during the syntheses of β-*O*-4 dilignols (**1**)–(**4**)

Substance	a	b	c	d	e	f	Overall yield (%)
	Yield (%)						
	Reaction time (min)						
S-S (**1**)	80.4		93.1	87.5		99.1	64.9
	10	30	35	85	5	4200	
S-G (**2**)	80.4		77.9	69.0		89.1	38.6
	10	30	130	40	10	1560	
G-S (**3**)	93.3	83.6	93.0	67.1		97.7	47.5
	15	60	540	270	5	2040	
G-G (**4**)	93.3	83.6	72.0	86.4		83.5	40.5
	15	60	210	90	10	1560	

S-S (**1**): 1,3-dihydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)-2-(2,6-dimethoxyphenoxy)propane
S-G (**2**): 1,3-dihydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)-2-(2-methoxyphenoxy)propane
G-S (**3**): 1,3-dihydroxy-2-(2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl)propane
G-G (**4**): 1,3-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propane

present case, ethyl acetate can be used instead of diethyl ether as an extraction solvent. Kawai et al.[14] reported this condition for the replacement reaction of brominated polyethyleneglycol with phenolic β-*O*-4 dilignols.

Steps (**d**) and (**e**) were carried out as described previously.[12,14,19] Cleavage of the benzoyl group (step **f**) was performed under the mild aminolysis condition.[20] A more drastic condition may cause a shorter reaction time.

Yields and reaction times of steps (**a**)–(**f**) during the syntheses of various β-*O*-4 dilignols (**1**)–(**4**) are shown in Table 1. Each reaction yielded more than 67%, and reaction times were relatively short, except for the debenzoylation (**f**). The reaction proceeded below ambient temperature without strict anhydrous and drastic conditions or chloric solvents. This route is applicable not only to phenolic β-*O*-4 dilignols but also to nonphenolic β-*O*-4 dilignols.[21]

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