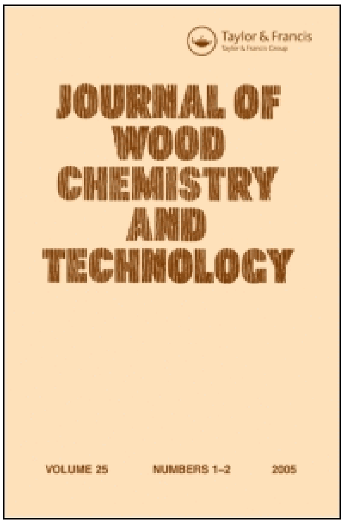

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Synthesis of Bromoacetophenone Derivatives as Starting Monomers for β-*O*-4 Type Artificial Lignin Polymers

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Synthesis of Bromoacetophenone Derivatives as Starting Monomers for β-O-4 Type Artificial Lignin Polymers

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Abstract: Guaiacyl, syringyl, and *p*-hydroxyphenyl-type bromoacetophenone derivatives were synthesized as the starting materials for β-O-4 type artificial lignin polymers. They were prepared from 4-hydroxyacetophenone instead of 4-hydroxybenzaldehyde, which was used in the previous investigations. The new route required 4 reaction steps. Overall yields of the monomers were 60, 79, and 68%, respectively.

Keywords: β-O-4 bond, linear polymer, model compounds, polymerization, Williamson ether formation

INTRODUCTION

The β-O-4 linkage is the most abundant and the most important substructure in lignin. In order to investigate the reactivity and chemical and physical property of lignin, lignin model compounds have been used frequently. Especially, β-O-4 type lignin model dimers attract special attention. We recently reported the chemical synthesis of artificial lignin polymer composed exclusively of the β-O-4 substructure.[1,2] The polymers are linear polymer with well-defined structures. They can be used as polymeric lignin model compounds.[3] It may be easy to analyze structural changes of the polymers caused by various treatments such as pulping, bleaching, biodegradation, and so on.

The synthesis of the β-O-4 type artificial lignin polymer consists of two key steps: (1) polycondensation of a brominated monomer by Williamson ether

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A part of this study was presented at the 50th Lignin Symposium in Nagoya, Japan (October 2005).

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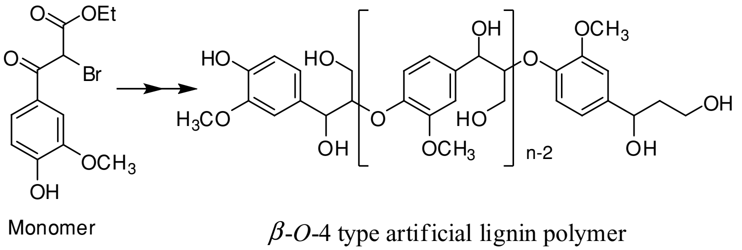


Figure 1. Synthesis of β-*O*-4 type artificial lignin polymer.

formation and (2) subsequent reduction of the carbonyl polymer as shown in Figure 1.[2] The guaiacyl type monomer was synthesized from 4-hydroxy-3-methoxybenzaldehyde (vanillin) in the previous investigation,[2] which required 7 reaction steps. In this investigation, synthetic procedure for the monomer was improved in order to decrease the reaction steps, and guaiacyl, syringyl and *p*-hydoroxyphenyl type monomers **5a–c** were synthesized as starting materials for β-*O*-4 type artificial lignin polymers (Figure 2).

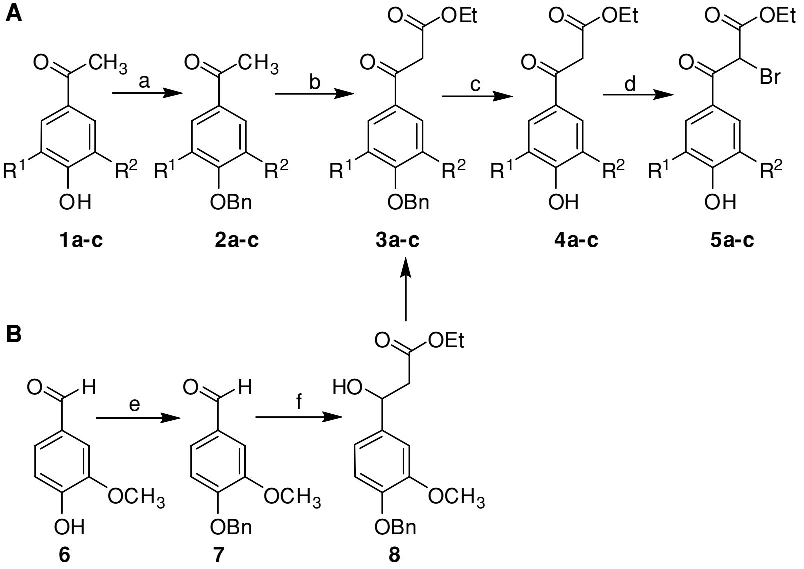
EXPERIMENTAL

Measurements

^{1}H- and ^{13}C- NMR spectra were recorded with a JEOL JNM EX-270 FT-NMR (270 MHz), a Bruker AVANCE II 400 FT-NMR (400 MHz) or a Bruker AMX500 FT-NMR (500 MHz) spectrometer in chloroform-*d* with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) and coupling constants are reported in δ-values (ppm) and Hz, respectively. EI-MS and high resolution EI-MS were done with JEOL JMS-SX102A or JEOL JMS AX-500, and high resolution ESI-ToF-MS was done with a Bruker micrOTOF.

Synthesis in Route A

1-(4-(Benzyloxy)-3-methoxyphenyl)ethanone (**2a**), 1-(4-(benzyloxy)-3,5-dimethoxyphenyl)ethanone (**2b**), and 1-(4-(benzyloxy)phenyl) ethanone (**2c**). To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone (**1a**) (16.6 g, 0.1 mol) in DMF (150 mL), benzyl chloride (13.8 mL, 0.12 mol), potassium carbonate (21 g, 0.15 mol) and tetra-*n*-butyl ammonium iodide (3.69 g, 0.01 mol) were added at room temperature. The reaction mixture was kept at room temperature over night. The reaction mixture was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4,



1a, **2a**, **3a**, **4a**, **5a**: $R^1 = H$, $R^2 = OCH_3$
1b, **2b**, **3b**, **4b**, **5b**: $R^1 = OCH_3$, $R^2 = OCH_3$
1c, **2c**, **3c**, **4c**, **5c**: $R^1 = H$, $R^2 = H$

Figure 2. Synthesis of monomers **5a–c**.

and concentrated to dryness in *vacuo*. The product was recrystallized from ethanol/hexane (1/4, *v*/*v*) to afford colorless crystals. Compounds **2b** and **2c** were synthesized from 1-(4-hydroxy-3,5-dimethoxyphenyl) ethanone (**1b**) (4.90 g, 0.025 mol) and 1-(4-hydroxyphenyl)ethanone (**1c**) (13.6 g, 0.1 mol), respectively, by the similar procedure, but at 50°C over night for **2b**. Compound **2a**: (23.21 g, 90.7%): ^{1}H-NMR ($CDCl_3$): δ2.54 (s, 3H, Cβ-H), 3.94 (s, 3H, OCH_3), 5.23 (s, 2H, $C\underline{H}_2C_6H_5$), 6.89 (d, 1H, $J = 8.4$, C5-H), 7.25–7.55 (m, 7H, aromatics); ^{13}C-NMR ($CDCl_3$): δ26.2 (Cβ), 56.1 (OCH_3), 70.8 ($\underline{C}H_2C_6H_5$), 110.5, 112.1, 123.1, 127.2, 128.1, 128.7, 130.7, 136.3, 149.5, 152.4 (aromatics), 196.8 (Cα); High resolution ESI-ToF-MS: m/z (M+ H^+): Calculated for $C_{16}H_{17}O_3$: 257.1172, found: 257.1170; (M+ Na^+): Calculated for $C_{16}H_{16}NaO_3$: 279.0992, found: 279.0986. Compound **2b**: (6.40 g, 89.5%): ^{1}H-NMR ($CDCl_3$): δ2.58 (s, 3H, Cβ-H), 3.88 (s, 6H, OCH_3), 5.10 (s, 2H, $C\underline{H}_2C_6H_5$), 7.20 (s, 2H, C2-H, C6-H), 7.24–7.48 (m, 5H, aromatics); ^{13}C-NMR ($CDCl_3$): δ26.4 (Cβ), 56.3 (OCH_3), 75.0 ($\underline{C}H_2C_6H_5$), 105.8, 128.0, 128.2, 128.4, 132.6, 137.3, 141.4, 153.3 (aromatics), 197.0 (Cα); High resolution ESI-ToF-MS: m/z (M+H^+): Calculated for $C_{17}H_{19}O_4$: 287.1278, found: 287.1279; (M+Na^+): Calculated for $C_{17}H_{18}NaO_4$: 309.1097, found: 309.1098. Compound **2c**: (21.86 g, 96.7%): ^{1}H-NMR ($CDCl_3$): δ2.55 (s, 3H, Cβ-H), 5.13

(s, 2H, $C\underline{H}_2C_6H_5$), 7.01 (d, 2H, $J = 8.9$, C3-H, C5-H), 7.93(d, 2H, $J = 8.9$, C2-H, C6-H), 7.32–7.45 (m, 5H, $CH_2C_6\underline{H}_5$); ^{13}C-NMR ($CDCl_3$): δ26.4 (Cβ), 70.1 ($\underline{C}H_2C_6H_5$), 114.5, 127.5, 128.2, 128.7, 130.5, 130.6, 136.2, 162.6 (aromatics), 196.8 (Cα); High resolution ESI-ToF-MS: m/z (M+H$^+$): Calculated for $C_{15}H_{15}O_2$: 227.1067, found: 227.1066; (M+Na$^+$): Calculated for $C_{15}H_{14}NaO_2$: 249.0886, found: 249.0884.

Ethyl 3-(4-(benzyloxy)-3-methoxyphenyl)-3-oxopropanoate (**3a**), and ethyl 3-(4-(benzyloxy)-3,5-dimethoxyphenyl)-3-oxopropanoate (**3b**), and ethyl 3-(4-(benzyloxy)phenyl)- 3-oxopropanoate (**3c**). To a stirred suspension of sodium hydride (6 g, 60–72% suspension in mineral oil) in anhydrous toluene (60 mL), ethyl carbonate (12.1 ml, 0.1 mol) was added at room temperature. Compound **2a** (12.8 g, 50.0 mmol) in anhydrous toluene (60 mL) was added drop-wise to the reaction mixture over a period of 2.5 h under reflux. After stirring for 0.5 h under reflux, the reaction mixture was cooled to room temperature, and acetic acid was added until the mixture became neutral. The reaction mixture was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated to dryness *in vacuo*. The product was triturated with hexane to afford a solid. The product was recrystallized from ethanol to afford crystals (13.57 g, 82.8%). Compounds **3b** and **3c** were synthesized by the similar procedure from compounds **2b** (2.56 g, 8.95 mmol) and **2c** (13.56 g, 60 mmol), respectively. Compound **3a**: (13.57 g, 82.8%): ^{1}H-NMR ($CDCl_3$): δ1.25 (t, 3H, $J = 7.0$, $OCH_2C\underline{H}_3$), 3.92 (s, 2H, Cβ-H), 3.93 (s, 3H, OCH_3), 4.20 (q, 2H, $J = 7.0$, $OC\underline{H}_2CH_3$), 5.20 (s, 2H, $C\underline{H}_2C_6H_5$), 6.90 (d, 1H, $J = 8.3$, C5-H), 7.23–7.59 (m, 7H, aromatics); ^{13}C-NMR ($CDCl_3$): δ14.1 ($OCH_2\underline{C}H_3$), 45.7 (Cβ), 56.1 (OCH_3), 61.4 ($O\underline{C}H_2CH_3$), 70.8 ($\underline{C}H_2C_6H_5$), 110.7, 112.1, 123.3, 127.2, 128.2, 128.7, 129.5, 136.1, 149.7, 153.0 (aromatics), 167.7 (Cγ), 191.0 (Cα); High resolution ESI-ToF-MS: m/z (M+Na$^+$): Calculated for $C_{19}H_{20}NaO_5$: 351.1203, found: 351.1180. Compound **3b**: (3.08 g, 96.5%): ^{1}H-NMR ($CDCl_3$): δ1.26 (t, 3H, $J = 7.1$, $OCH_2C\underline{H}_3$), 3.87 (s, 6H, OCH_3), 3.95 (s, 2H, Cβ-H), 4.21 (q, 2H, $J = 7.1$, $OC\underline{H}_2CH_3$), 5.11 (s, 2H, $C\underline{H}_2C_6H_5$), 7.19 (s, 2H, C2-H, C6-H), 7.28–7.48 (m, 5H, $CH_2C_6\underline{H}_5$); ^{13}C-NMR ($CDCl_3$): δ14.1 ($OCH_2\underline{C}H_3$, 46.1 (Cβ), 56.3 (OCH_3), 61.5 ($O\underline{C}H_2CH_3$), 75.0 ($\underline{C}H_2C_6H_5$), 106.1, 128.1, 128.2, 128.4, 131.3, 137.2, 142.0, 153.5 (aromatics), 167.5 (Cγ), 191.2 (Cα); High resolution ESI-ToF-MS: m/z (M+Na$^+$): Calculated for $C_{20}H_{22}NaO_6$: 381.1309, found: 381.1302. Compound **3c**: (16.95 g, 94.8%): ^{1}H-NMR ($CDCl_3$): δ1.26 (t, 3H, $J = 7.1$, $OCH_2C\underline{H}_3$), 3.94 (s, 2H, Cβ-H), 4.21 (q, 2H, $J = 7.1$, $OC\underline{H}_2CH_3$), 5.14 (s, 2H, $C\underline{H}_2C_6H_5$), 7.02 (d, 2H, $J = 8.8$, C3-H, C5-H), 7.92(d, 2H, $J = 8.8$, C2-H, C6-H), 7.30–7.50 (m, 5H, $CH_2C_6\underline{H}_5$); ^{13}C-NMR ($CDCl_3$): δ14.1 ($OCH_2\underline{C}H_3$), 45.8 (Cβ), 61.4 ($O\underline{C}H_2CH_3$), 70.2 ($\underline{C}H_2C_6H_5$), 114.8, 127.5, 128.3, 128.7, 129.3, 130.9, 136.0, 163.1 (aromatics), 167.7 (Cγ), 191.0 (Cα); High resolution ESI-ToF-MS: m/z (M+Na$^+$): Calculated for $C_{18}H_{18}NaO_4$: 321.1097, found: 321.1081.

Ethyl 3-(4-hydroxy-3-methoxyphenyl)-3-oxopropanoate (**4a**), ethyl 3-(4-hydroxy-3,5-dimethoxyphenyl)-3-oxopropanoate (**4b**) and ethyl 3-

(**4**-hydroxyphenyl)-3-oxopropanoate (**4c**). A stirred solution of compound **3a** (2.835 g) in ethanol (60 mL) was treated with 10% palladium carbon (300 mg) under H_2 at 0°C for 2.5 h. The reaction mixture was filtered and concentrated to dryness *in vacuo*. The product was purified on a silica gel column with ethyl acetate/hexane (1/2, *v*/*v*) to afford a syrup (**4a**, 2.00 g, 97.2%). Compounds **4b** and **4c** were synthesized from compound **3b** (1.02 g, 2.84 mmol) and **3c** (15 g, 0.05 mol), respectively, by the similar procedure, but at –5–10°C for **4c**. Compound **4a**: (2.00 g, 97.2%): ^{1}H-NMR ($CDCl_3$): δ1.26 (t, 3H, J = 7.0, $OCH_2C\underline{H}_3$), 3.94 (s, 2H, Cβ-H), 3.95 (s, 3H, OCH_3), 4.21 (q, 2H, J = 7.0, $OC\underline{H}_2CH_3$), 6.95 (d, 1H, J = 8.1, C5-H), 7.50 (dd, 1H, J = 8.1, J = 1.8, C6-H), 7.54 (d, 1H, J = 1.8, C2-H); ^{13}C-NMR ($CDCl_3$): δ14.1 ($OCH_2\underline{C}H_3$), 45.7 (Cβ), 56.1 (OCH_3), 61.5 ($O\underline{C}H_2CH_3$), 110.1, 114.0, 124.2, 129.0, 146.8, 151.0 (aromatics), 167.8 (Cγ), 191.0 (Cα); High resolution ESI-ToF-MS: m/z ($M+Na^+$): Calculated for $C_{12}H_{14}NaO_5$: 261.0733, found: 261.0723. Compound **4b**: (0.72 g, 94.3%): ^{1}H-NMR ($CDCl_3$): δ1.27 (t, 3H, J = 7.1, $OCH_2C\underline{H}_3$), 3.96 (s, 2H, Cβ-H), 3.96 (s, 6H, OCH_3), 4.22 (q, 2H, J = 7.1, $OC\underline{H}_2CH_3$), 7.26 (s, 2H, C2-H, C6-H); ^{13}C-NMR ($CDCl_3$): δ14.1 ($OCH_2\underline{C}H_3$), 46.0 (Cβ), 56.5 (OCH_3), 61.5 ($O\underline{C}H_2CH_3$), 106.0, 127.6, 140.3, 146.9 (aromatics), 167.7 (Cγ), 190.8 (Cα); High resolution ESI-ToF-MS: m/z ($M+H^+$): Calculated for $C_{13}H_{17}O_6$: 269.1020, found: 269.1014; ($M+Na^+$): Calculated for $C_{13}H_{16}NaO_6$: 291.0839, found: 291.0837. Compound **4c**: (crystals, 9.32 g, 89.0%): ^{1}H-NMR ($CDCl_3$): δ1.26 (t, 3H, J = 7.1, $OCH_2C\underline{H}_3$), 3.95 (s, 2H, Cβ-H), 4.22 (q, 2H, J = 7.1, $OC\underline{H}_2CH_3$), 6.88 (d, 2H, J = 8.7, C3-H, C5-H), 7.85 (d, 2H, J = 8.7, C2-H, C6-H); ^{13}C-NMR ($CDCl_3$): δ14.0 ($OCH_2\underline{C}H_3$), 45.7 (Cβ), 61.8 ($O\underline{C}H_2CH_3$), 115.7, 128.6, 131.3, 161.6 (aromatics), 168.4 (Cγ), 191.7 (Cα); High resolution ESI-ToF-MS: m/z ($M+Na^+$): Calculated for $C_{11}H_{12}NaO_4$: 231.0628, found: 231.0630.

Ethyl 2-bromo-3-(4-hydroxy-3-methoxyphenyl)-3-oxopropanoate (**5a**), ethyl 2-bromo-3-(4-hydroxy-3,5-dimethoxyphenyl)-3-oxopropanoate (**5b**) and ethyl 2-bromo-3-(4-hydroxyphenyl)-3-oxopropanoate (**5c**). To a stirred solution of compound 4a (2.10 g, 8.82 mmol) in chloroform (10 ml), a diluted solution of bromine (1.48 g, 9.26 mmol) in chloroform (10 ml) was added drop-wise over a period of 2.5 h at −5°C. The reaction mixture was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated to dryness *in vacuo*. The product was purified on a silica gel column with chloroform to afford colorless crystals (**5a**, 2.31 g, 82.6%). The crystals were further recrystallized from ethanol/hexane for polymerization in order to remove impurity completely. Compounds **5b** and **5c** were synthesized from compounds **4b** (3 g, 11.2 mmol) and **4c** (3 g, 14.4 mmol), respectively, by the similar procedure, but at 0°C both for **5b** and **5c**. Compound **5a:** (2.31 g, 82.6%): ^{1}H-NMR ($CDCl_3$): δ1.26 (t, 3H, J = 7.1, $OCH_2C\underline{H}_3$), 3.96 (s, 3H, OCH_3), 4.28 (q, 2H, J = 7.1, $OC\underline{H}_2CH_3$), 5.63 (s, 1H, Cβ-H), 6.97 (d, 1H, J = 8.6, C5-H), 7.56–7.59 (m, 2H, C2-H, C6-H); ^{13}C-NMR ($CDCl_3$): δ13.9($OCH_2\underline{C}H_3$46.2) (Cβ), 56.2 (OCH_3), 63.3 ($O\underline{C}H_2CH_3$), 110.0, 114.1, 124.7, 126.1, 146.9, 151.5 (aromatics), 165.4 (Cγ), 186.7 (Cα); EI-MS: m/z (rel. int.): 318 (4.1), 316 (M^+, 4.2), 238 (6.3), 152 (8.8), 151 (100), 123 (8.8), 44 (6.6), 40 (8.5); High resolution EI-MS: m/z (M^+): Calculated for $C_{12}H_{13}O_5Br$: 315.9946, found: 315.9955. Compound **5b**: (syrup, 3.76 g, 96.9%): ^{1}H-NMR ($CDCl_3$): δ1.26 (t, 3H, J = 7.1, $OCH_2C\underline{H}_3$), 3.96 (s, 6H, OCH_3), 4.29 (q, 2H, J = 7.1, $OC\underline{H}_2CH_3$), 5.61 (s, 1H, Cβ-H), 7.30 (s, 2H, C2-H, C6-H); ^{13}C-NMR ($CDCl_3$): δ14.0 ($OCH_2\underline{C}H_3$), 46.6 (Cβ), 56.5 (OCH_3), 63.3 ($O\underline{C}H_2CH_3$), 106.7, 124.7, 140.8, 146.9 (aromatics), 165.4 (Cγ), 186.5 (Cα); EI-MS: m/z (rel. int.): 348 (5.4), 346 (M^+, 5.8), 182 (10.3), 181 (100), 173 (26.7), 151 (11.3), 149 (16.1), 107 (11.9), 92 (16.1), 91 (22.2), 85 (15.2), 83 (22.5), 57 (10.2); High resolution EI-MS: m/z (M^+): Calculated for $C_{13}H_{15}O_6Br$: 346.0052, found: 346.0032. Compound **5c**: (3.45 g, 83.3%): ^{1}H-NMR ($CDCl_3$): δ1.27 (t, 3H, J = 7.1, $OCH_2C\underline{H}_3$), 4.29 (q, 2H, J = 7.1, $OC\underline{H}_2CH_3$), 5.63 (s, 1H, Cβ-H), 6.92 (d, 2H, J = 8.9, C3-H, C5-H), 7.94 (d, 2H, J = 8.9, C2-H, C6-H); ^{13}C-NMR ($CDCl_3$): δ13.9($OCH_2\underline{C}H_3$)46.1 (Cβ), 63.5 ($O\underline{C}H_2CH_3$), 115.9, 126.2, 132.1, 161.3 (aromatics), 165.6 (Cγ), 187.0 (Cα); EI-MS: m/z (rel. int.): 288 (3.4), 286 (M^+, 3.4), 122 (8.1), 121 (100), 40 (6.3); High resolution EI-MS: m/z (M^+): Calculated for $C_{11}H_{11}O_4Br$: 285.9841, found: 285.9861.

Synthesis in Route B

4-(Benzyloxy)-3-methoxybenzaldehyde (**7**): To a stirred solution of 4-hydroxy-3-methoxybenzaldehyde (**6**) (30.4 g, 0.2 mol) in DMF (300 mL), benzyl chloride (33.4 mL, 0.24 mol), potassium carbonate (42 g, 0.3 mol) and tetra-*n*-butyl ammonium iodide (3.69 g, 0.01 mol) were added at room temperature. The reaction mixture was kept at room temperature over night. The reaction mixture was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated to dryness *in vacuo*. The product was recrystallized from ethanol to afford colorless crystals (45.2 g, 90.7%). Compound **7**: ^{1}H-NMR ($CDCl_3$): δ3.95 (s, 3H, OCH_3), 5.25 (s, 2H, $C\underline{H}_2C_6H_5$), 6.99 (d, 1H, J = 8.2, C5-H), 7.30–7.46 (m, 7H, aromatics), 9.84 (s, 1H, Cα); ^{13}C-NMR ($CDCl_3$): δ56.1 (OCH_3), 70.9 ($\underline{C}H_2C_6H_5$), 109.3, 112.4, 126.6, 127.2, 128.2, 128.7, 130.3, 136.0, 150.1, 153.6 (aromatics), 190.9 (Cα); High resolution ESI-ToF-MS: m/z ($M+Na^+$): Calculated for $C_{15}H_{14}NaO_3$: 265.0835, found: 265.0820.

Ethyl 3-(4-(benzyloxy)-3-methoxyphenyl)-3-hydroxypropanoate (**8**): To a stirred suspension of zinc powder (490 mg) and CuBr (16.3 mg), 5.5 ml of Et_2Al solution in hexane (1 mol/l) was added at room temperature. 4-(Benzyloxy)-3-methoxybenzaldehyde (**7**) (1.21 g, 5 mmol) and ethyl 2-bromoacetate (0.55 ml, 5 mmol) were added drop-wise to the solution at 0°C. After 2 h, 1.5 ml of pyridine was added to the reaction mixture. The reaction mixture was diluted with ethyl acetate, washed with 2 mol/l HCl and brine, dried over Na_2SO_4, and concentrated to dryness in vacuo to afford a syrup (1.55 g, 94.0%). The product was pure enough to be used without purification for the following step.Compound **8**: ^{1}H-NMR ($CDCl_3$): δ1.26 (t, 3H, J = 7.0, $OCH_2C\underline{H}_3$), 2.61–2.81 (m, 2H, Cβ-H), 3.90 (s, 3H, OCH_3), 4.18 (q, 2H, $J = 7.0$, $OC\underline{H}_2CH_3$), 5.06 (m, 1H, Cα-H), 5.29 (s, 2H, $C\underline{H}_2C_6H_5$), 6.78–6.97, 7.25–7.45 (m, 8H, aromatics); ^{13}C-NMR ($CDCl_3$): δ14.2($OCH_2\underline{C}H_3$)43.4 (Cβ), 56.0 (OCH_3), 60.9 ($O\underline{C}H_2CH_3$), 70.2 (Cα), 71.0 ($\underline{C}H_2C_6H_5$), 109.4, 113.9, 117.9, 127.2, 127.8, 128.5, 135.8, 137.1, 147.7, 149.8 (aromatics), 172.4 (Cγ); High resolution ESI-ToF-MS: m/z ($M+Na^+$): Calculated for $C_{19}H_{22}NaO_5$: 353.1359, found: 353.1346.

Ethyl 3-(4-(benzyloxy)-3-methoxyphenyl)-3-oxopropanoate (**3a**). To a stirred solution of compound **8** (1.07 g) in a mixture of acetonitrile (10 ml) and water (1 ml), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.14 g) was added at room temperature. After stirring for 0.5h, the reaction mixture was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated to dryness *in vacuo*. The product was separated on a silica gel column with ethyl acetate/hexane (1/2, v/v) to afford compound **3a** (746 mg, 67%). The product contained small amount of hydroquinone derived from DDQ.

RESULTS AND DISCUSSION

Improvement of Synthetic Route for Guaiacyl Type Monomer

Compound **3a** has been synthesized by Kratzl and Miksche from 4-hydroxy-3-methoxybenzaldehyde (vanillin)[4] by the similar procedure employed by Bradley and Robinson for compound **3b**.[5] The synthesis includes (1) benzylation of vanillin, (2) oxidation to the benzoic acid derivative, (3) conversion to the acid chloride derivative, (4) coupling with ethyl acetoacetate, and (5) deacetylation. In our previous investigation, compound **3a** was prepared by the method of Kratzl and Miksche, and was converted to the guaiacyl type monomer **5a** by debenzylation followed by bromination with $CuBr_2$.[2] The synthetic route may be applicable to the large-scale synthesis.[4] However, the route for the monomer still requires 7 reaction steps from vanillin.

In order to improve the synthetic route for the monomer, two reaction pathways were examined as shown in Figure 2. In route A, 4-hydroxy-3-methoxyacetophenone (**1a**) was used as a starting material. Compound **1a** was benzylated with benzyl chloride and potassium carbonate in dimethyl formamide (DMF) to afford compound **2a** in 91% yield. Condensation between compound **2a** and ethyl carbonate by lithium diisopropyl amide (LDA) at −78°C resulted in the recovery of the starting material. However, condensation of them by sodium hydride was successfully conducted under the similar conditions reported for the synthesis of 2-carbethoxycyclooctanone.[6] The yield of compound **3a** from **2a** was 83%. Synthesis of methyl analog of compound **3a** by the similar procedure was also reported recently,[7] while we were preparing syringyl and *p*-hydroxyphenyl type monomers.

Reduction of compound **3a** to compound **4a** with H_2 in the presence of palladium charcoal could be performed without reduction of the carbonyl group at α-position in 97% yield, when the treatment was conducted at 0°C.[2] We tried to synthesize compound **4a** directly from compound **1a** by condensation with ethyl carbonate without protection of phenolic hydroxyl group. The condensation by sodium hydride under reflux in anhydrous toluene failed. LDA at -78°C in anhydrous tetrahydrofuran (THF) did not work either, and both conditions resulted in the recovery of the starting material. Stronger base, lithium bistrimethylsilylamide (LHMDS) worked better. However, the reaction did not proceed completely, and the mixture of compound **1a** and **4a** was recovered. The yield of compound **4a** was about 35%, which was estimated from ^{1}H-NMR spectrum of the reaction mixture without separation, because compound **4a** could not be separated from compound **1a** by a silica gel column with ethyl acetate/*n*-hexane (1:2, *v*/*v*). It may be possible to increase the yield of compound **4a**, if some other conditions or bases were used. However, further experiments were not conducted in this investigation.

Bromination procedure of compound **4a** was modified from the previous investigation, as well.[2] Compound **4a** was treated with bromine in chloroform at -5°C instead of $CuBr_2$in ethyl acetateto give compound **5a** in 83% yield. For large-scale synthesis, bromine is more efficient than $CuBr_2$ and higher yield can be achieved. Overall yield of compound **5a** from compound **1a** was 60% with 4 reaction steps in route A, which is almost the same as that from vanillin in the previous route with 7 reaction steps (62%).

On the other hand, vanillin (**6**) was used as a starting material in route B. Compound **6** was benzylated with benzyl chloride and potassium carbonate in DMF to give 4-(benzyloxy)-3-methoxybenzaldehyde (**7**) in 91% yield. Ethyl 3-(4-(benzyloxy)- 3-methoxyphenyl)-3-hydroxypropanoate (**8**) can be prepared by the coupling between compound **7** and ethyl acetate with LDA in anhydrous THF (aldol type condensation) in 94% yield.[8] Coupling between compound **7** and ethyl 2-bromoacetate by zinc powder (Reformatsky reaction) in the presence of Et_2Al and CuBr in anhydrous THF[9] gave compound **8** in high yield (94%), as well. However, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of compound **8** resulted in moderate yield (70%). The syrupy materials of hydroquinone derived from DDQ could not be removed completely from the reaction mixture by the repeated separation with silica gel column chromatography.

Overall yield of compound **5a** from compound **7** in route B was 48%, which is lower than that from compound **1a** in route A (60%). Route B required 5 reaction steps, and was more tedious than route A. Thus, route A was used for the synthesis of syringyl and *p*-hydoroxyphenyl type monomers in the following investigation.

Synthesis of Syringyl and p-Hydroxyphenyl Type Monomers

Syringyl and *p*-hydroxyphenyl type monomers **5b** and **5c** were synthesized from 4-hydroxy 3,5-dimethoxy acetophenone (**1b**) and 4-hydroxy acetophenone (**1c**), respectively, by the similar procedure for monomer **5a** (Route A). Overall yields of compounds**5a**, **5b**, and **5c** from compounds **1a**, **1b**, and **1c** were 60, 79, 68%, respectively. Compounds **5a** and **5c** were obtained as crystals but compound **5b** was a syrup. All of these monomers can be used as starting materials for the synthesis of β-O-4 type artificial lignin polymers.

REFERENCES

1. Kishimoto, T.; Uraki, Y.; Ubukata, M. Easy synthesis of β-O-4 type lignin related polymers. Org. Biomol. Chem. **2005**, *3*, 1067–1073.
2. Kishimoto, T.; Uraki, Y.; Ubukata, M. Chemical synthesis of β-O-4 type artificial lignin. Org. Biomol. Chem. **2006**, *4*, 1343–1347.
3. Saito, K.; Kato, T.; Takamori, H.; Kishimoto, T.; Yamamoto, A.; Fukushima, K. A new analysis of the depolymerized fragments of lignin polymer in the plant cell walls using ToF-SIMS. Applied Surface Science. **2006**, *252*, 6734–6737.
4. Kratzl, K; Miksche, G.E. Zur Synthese des dl-Pinoresinols. Monatshefte fuer Chemie. **1963**, *94*(2), 434–439.
5. Bradley, W.R.; Robinson, R. A synthesis of pyrylium salts of anthocyanidin type. Part XVIII. A synthesis of malvidin chloride. J. Chem. Soc. **1928**, 1541–1569.
6. Krapcho, P.; Diamanti, J.; Cayen, C.; Bingham, R. In *Organic Syntheses*; Danheiser, R.L. et al., Eds., Vol. 47, 1967; 20.
7. Schatz, P.F.; Ralph, J.; Lu, F.; Guzei, I.A.; Bunzel, M. Synthesis and identification of 2,5-bis-(4-hydroxy-3-methoxyphenyl)-tetrahydrofuran-3,4-dicarboxylic acid, an unanticipated ferulate 8-8-coupling product acylating cereal plant cell walls. Org. Biomol. Chem. **2006**, *4*, 2801–2806.
8. Ciofi-Baffoni, S.; Banci, L.; Brandi, A. Synthesis of oligomeric mimics of lignin. J. Chem. Soc., Perkin Trans. 1, **1998**, 3207–3217.
9. Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. A new and highly effective aldol synthesis. Bull. Chem. Soc. Jpn. **1980**, *53*, 3301–3307.