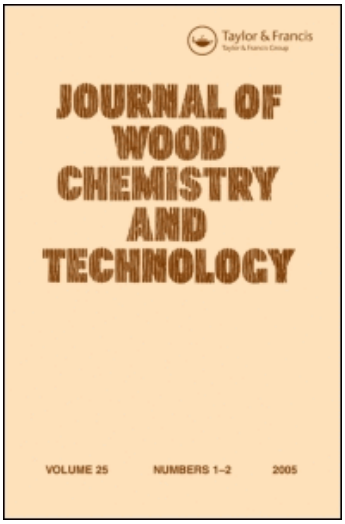

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Studies on the Dehydrogenative Polymerizations of Monolignol β-Glycosides. Part 1. Syntheses of Monolignol β-glycosides, (*E*)-Isoconiferin, (*E*)-Isosyringin, and (*E*)-Triandrin

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Studies on the Dehydrogenative Polymerizations of Monolignol β-Glycosides. Part 1. Syntheses of Monolignol β-glycosides, (*E*)-Isoconiferin, (*E*)-Isosyringin, and (*E*)-Triandrin

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Abstract: (*E*)-4-*O*-Acetyl coniferyl alcohol was synthesized by the reduction of (*E*)-4-*O*-acetyl ferulic acid with sodium borohydride and *N,N*-dimethylchloromethylenium chloride in 80.2% yield. The glycosylation of (*E*)-4-*O*-acetyl coniferyl alcohol with trichloroacetimidoyl 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranoside in the presence of BF_3-Et_2O in anhydrous CH_2Cl_2, followed by deacylation gave (*E*)-isoconiferin in high yield. This synthetic method could be applied to the syntheses of other monolignol β-glycosides. As a result, (*E*)-isoconiferin, (*E*)-isosyringin, and (*E*)-triandrin were

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synthesized from vanillin, syringaldehyde, and p-hydroxybenzaldehyde, respectively, by five reaction steps in high overall yield.

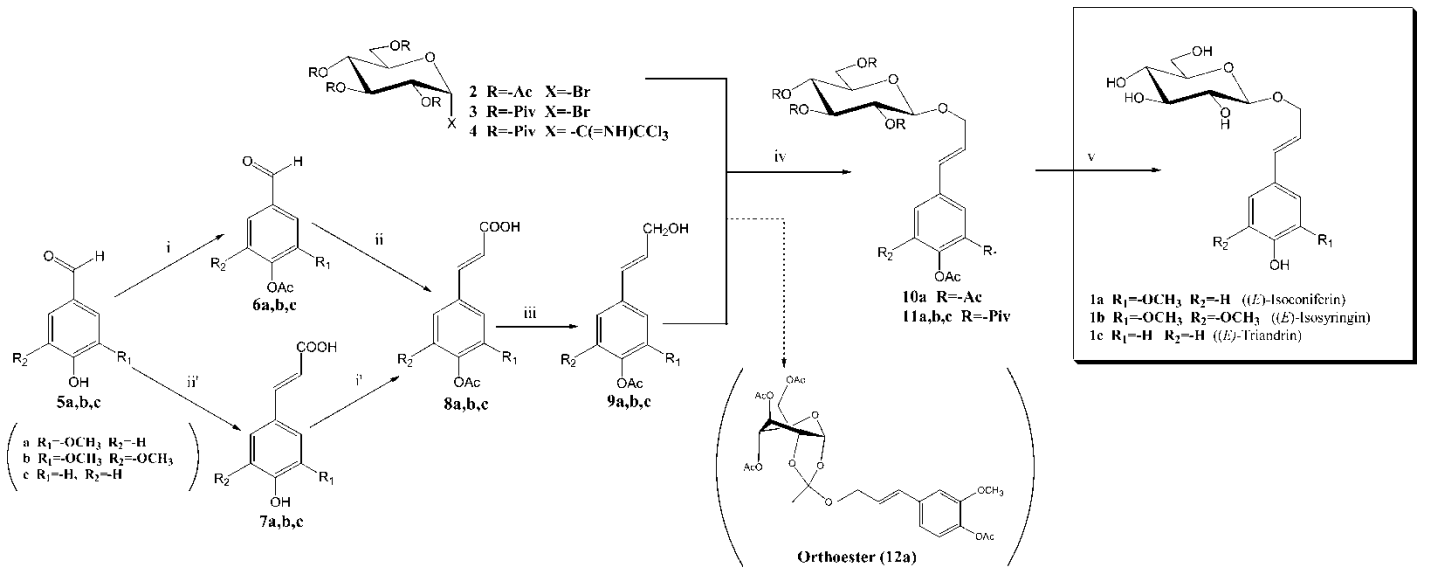
Keywords: Lignin, DHP, isoconiferin, isosyringin, triandrin, imidate method

INTRODUCTION

Dehydrogenative polymer (DHP), which has been widely used as a lignin model polymer, was prepared by dehydrogenative polymerization of monolignols, such as (*E*)-coniferyl alcohol, (*E*)-sinapyl alcohol, and (*E*)-*p*-coumaryl alcohol. In the polymerization, the γ-hydroxyl group of the monolignol does not directly participate in radical coupling, although it can effect nucleophilic addition to the quinonemethide to form a pinoresinol unit. If a new functional group is introduced at the γ-position of the monolignol, a new lignin–like polymer will be obtained on dehydrogenative polymerization.

In this study, D-glucose was selected as the new functional group for γ-position, that is, monolignol β-glucosides were the functional monolignols. This choice was made for the following reasons. First, it was expected that high molecular weight, water-soluble DHP could be obtained on dehydrogenative polymerization of monolignol β-glucosides. The molecular weight of DHPs from monolignols by the conventional method are much lower than that of native lignin,[1] although Tanahashi and Higuchi reported that a highly polymerized DHP could be isolated by a dialysis membrane method.[2] This might be caused by the resulting DHP precipitating from the solution at the beginning of the polymerization, and the subsequent polymerization must proceed in a heterogeneous system. However, on polymerization of monolignol β-glucosides, it was expected that the hydrophilicity of the D-glucose moiety would prevent the DHP from precipitating, and the polymerization would proceed in a homogeneous system. Kondo et al. reported that dehydrogenative copolymerization of coniferyl alcohol and (*E*)-isoconiferin gave water-soluble DHP, although the degree of polymerization of the resulting DHP was not described in detail.[3] Second, it was also of interest whether the lignin part of the DHP from monolignol β-glucosides might be optically active because of the chirality introduced by the D-glucose moiety. Third, the chemical and physical properties of the DHP from monolignol β-glucosides would be of interest in comparison with lignin carbohydrate complexes (LCC), because a glycosidic linkage is thought to be one of the linkages of LCC.[4] Fourth, monolignol β-glycosides have been found in nature and are therefore compounds of interest.

The compounds in which D-glucose is connected at the γ-position of coniferyl alcohol, sinapyl alcohol, and *p*-coumaryl alcohol are isoconiferin, isosyringin, and triandrin, respectively (see Figure 1), although there are two isomers (*E* and *Z*) depending on the configuration of the monolignol.



i or i' Ac_2O / Pyridine / r.t. / 4 h. ii or ii' $HOOCCH_2COOH$ / Pyridine / Aniline/ 50°C / overnight. iii $(COCl)_2$ / anhydrous DMF / 0°C / 1h ; $NaBH_4$ / anhydrous DMF / -78°C / 2 h. iv $Hg(CN)_2$ / anhydrous CH_2ClCH_2Cl / 50°C / 4.5 h or $.BF_3$-Et_2O / anhydrous CH_2Cl_2/ -60°C / 2 h. v 28%-NaOMe in MeOH / MeOH / 0°C / 4 h.

Figure 1. Synthetic routes for (*E*)-isoconiferin (1a), (*E*)-isosyringin (1b), (*E*)-triandrin (1c).

(*E*)-Isoconiferin (1a) has been isolated from *Citrus unshiu* peel as citrusin D.[5] Recently, it was also found in the stem of *Cynomorium songaricum*,[6] and in the aerial parts of *Juniperus communis var. depressa.*[7] It has been reported that this compound lowers blood pressure.[8] (*Z*)-Isoconiferin was isolated from the bark of beech (*Fagus sylvatica, Fagus grandifolia*) as faguside.[9–12] Its insecticidal activity and its activity as an inducer of eclosion have been reported.[12] (*E*)-Isosyringin (1b) was isolated with (*E*)-isoconiferin from *Zantedeschia aethiopica*[13] or from *Pistia stratiotes*.[14] (*E*)-Triandrin (1c) was isolated from the barks or twigs of willow (*Salix*) species (*Salix triandra L., Salix viminalis L., Salix phyilicifolia, Salix mysinifollia, Salix pentandra, Salix acutifolia*).[15–19] It was also isolated from the male inflorescence of *Sarcophyte sanguinea.*[20] (*Z*)-Triandrin was reported to be isolated from *Saxifraga stellaris*, although analytical data for it was not described.[21]

There are several reports of syntheses of (*E*)-isoconiferin (1a),[22–26] although the syntheses of (*E*)-isosyringin (1b) and (*E*)-triandrin (1c) have not been reported. Ibrahim reported that the glycosylation of coniferyl alcohol with UDP-glucose by glucosyltransferase, extracted from *Forsythia ovata*, gave compound **1a** in 20∼30% yield, although details of the structural determination were not described.[22] Kondo et al. reported that (*E*)-isoconiferin (1a) was synthesized from (*E*)-coniferyl alcohol in a cellobiose culture by a commercial β-glucosidase in 28.6% yield.[23] However, it was not clear whether these enzymatic synthetic methods were applicable to monolignols other than coniferyl alcohol. Lewis et al. reported that a mixture of (*E*) and (*Z*)-isoconiferin was obtained in 19.4% yield by the photo-isomerization of (*Z*)-isoconiferin isolated from beech bark.[24] Matsushita et al. reported that glycosylation of tetrahydropyranyl ether of (*E*)-coniferyl alcohol with 1,2-anhydro-3,4,6-tri-O-pivaloyl-α-D-glucopyranose in the presence of SiO_2 gave the (*E*)-isoconiferin derivative.[25] The yield in the glycosylation was moderate (65%).

This article describes the first step of a study on dehydrogenative polymerization of monolignol β-glucosides, namely the high yield synthesis of (*E*)-isoconiferin (1a), (*E*)-isosyringin (1b), and (*E*)-triandrin (1c).

MATERIALS AND METHODS

General

Melting points were measured by a Mettler FP82HT hot stage and a Mettler FP90 central processor. Optical rotations were recorded at ambient temperature with a Jasco DIP 1000 polarimeter. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Varian INOVA 300 FT-NMR (300 MHz, 75 MHz) with tetramethylsilane (TMS) as an internal standard in $CDCl_3$, $(CD_3)_2CO$, or CD_3OD. Chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. All peaks were assigned by gCOSY, gHSQC, and gHMBC

spectroscopy. In most cases, the γ-protons (Ar-CH = CH-CHaHb-) of a monolignol unit of the glycoside were non-equivalent. Each of these protons appear as ddd with coupling to each other, the β-proton, and the α-proton.

All chemicals were purchased from Nacalai Tesque, Inc (Kyoto, Japan) or Wako Pure Chemical Industries (Osaka, Japan), and used as supplied, unless otherwise noted. Anhydrous *N,N*-dimethylformamide (DMF) and anhydrous tetrahydrofuran (THF) were prepared by distillation from CaH_2 and potassium, respectively. Anhydrous CH_2Cl_2, CH_2ClCH_2Cl, and CH_3CN were prepared by distillation from P_2O_5.

(*E*)-3-(4-Acetoxy-3-methoxyphenyl)-2-propen-1-ol (9a)

Oxalyl Chloride (3.5 mL, 40 mM) was added slowly to anhydrous DMF (13 mL) at 0°C. After the reaction mixture was stirred at 0°C for 1 h, the solvent was removed at reduced pressure. A solution of (*E*)-3-(4-acetoxy-3-methoxyphenyl)-2-propenic acid (8a, 4.72 g, 20 mM) in anhydrous DMF (25 mL) was added at −40°C to the white residue. The reaction mixture was kept at the same temperature for 1 h. A suspension of $NaBH_4$ (3.04 g, 80 mM) in anhydrous DMF (20 mL) was added drop wise to the reaction mixture at −78°C and the temperature was slowly raised to room temperature for 2 h. Then, aqueous 4*N* HCl (60 mL) was added. The reaction mixture was extracted with EtOAc several times until compound 9a was not detected on TLC analysis. The combined EtOAc layers were washed with saturated $NaHCO_3$ solution and then brine, and finally dried over anhydrous Na_2SO_4. Evaporation *in vacuo* produced a yellowish oil, which was purified by a silica gel column chromatography (eluent: EtOAc/*n*-hexane (1/2 (v/v)) to give compound 9a as a colorless oil (3.56 g, 80.2% yield). ^{1}H-NMR and ^{13}C-NMR data of the product were in agreement with the known data of compound 9a.[27,28]

(*E*)-3-(4-Acetoxy-3,5-dimethoxyphenyl)-2-propen-1-ol (9b)

Compound 9b was synthesized from (*E*)-3-(4-acetoxy-3,5-dimethoxyphenyl)-2-propenic acid (8b) in a manner similar to compound 9a in 73.7% yield; mp; 87–88°C (lit. 85–86°C).[27] ^{1}H-NMR and ^{13}C-NMR data of the product were in agreement with reported data for compound 9b.[27,28]

(*E*)-3-(4-Acetoxyphenyl)-2-propen-1-ol (9c)

(*E*)-3-(4-Acetoxyphenyl)-2-propenic acid (8c) was reacted by the methods used to prepare compound 9a to give compound 9c in 82.5% yield; mp; 69–70°C (lit. 68–70°C).[27] ^{1}H-NMR and ^{13}C-NMR data of the product were in agreement with reported data for compound 9c. [27]

(*E*)-3-(4-Acetoxy-3-methoxyphenyl)-2-propen-1-yl 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranoside (11a)

Method A (Helferich Modification Method)

2,3,4,6-Tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide (3)[29] (14.5 g, 25 mM), compound 9a (3.71 g, 16.7 mM), $Hg(CN)_2$ (6.75 g, 26.7 mM) and molecular sieve 4A (13.4 g) were dried in a flask *in vacuo* for 6 h. Anhydrous CH_2ClCH_2Cl (120 mL) was added to the flask. The reaction mixture was stirred at 50°C for 4.5 h and filtered. The filtrate was extracted with EtOAc, washed with a saturated $NaHCO_3$ and then with brine, and finally dried over anhydrous Na_2SO_4. Evaporation *in vacuo* produced a crude product, which was purified by a silica gel column chromatography (eluent: EtOAc/*n*-hexane (1/4 (v/v)) to give compound 11a as colorless crystals (9.88 g, 82.1% yield).

Method B (Imidate Method)

Trichloroacetoimidoyl 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranoside (4)[30] (6.70 g, 10.1 mM), compound 9a (1.50 g, 6.76 mM) and molecular sieves 4A (5.0 g) were dried in a flask *in vacuo* for 6 h. Anhydrous CH_2Cl_2 (40 mL) was added to the flask. After the reaction mixture was cooled to −60°C, BF_3-Et_2O (212 μl, 1.67 mM) was added. The reaction mixture was stirred at same temperature for 1.5 h, and filtered. The filtrate was extracted with EtOAc, washed with a saturated $NaHCO_3$ solution and then with brine, and finally dried over anhydrous Na_2SO_4. Evaporation *in vacuo* produced a crude product, which was purified by a silica gel column chromatography (eluent: EtOAc/*n*-hexane (1/4 (v/v)) to give compound 11a as colorless crystals (4.58 g, 94.1% yield); mp; 131–132°C, $[\alpha]_D^{24}$; −6.1°(c = 1.0, $CHCl_3$), ^{1}H-NMR ($CDCl_3$); δ 7.27 (broad s, 1, H-2), 6.60 (broad s, 2, H-5, H-6), 6.51 (broad d, 1, J = 15.9, Ar-C<u>H</u> = CH), 6.14 (dt, 1, J = 15.9 and 5.1, Ar-CH = C<u>H</u>), 5.34 (t, 1, J = 9.6, H-3′), 5.14 (t, 1, J = 9.6, H-4′), 5.09 (dd, 1, J = 9.6 and 8.1, H-2′), 4.62 (d, 1, J = 8.1, H-1′), 4.50 (ddd, 1, J = 13.2, 5.1, and 1.5, Ar-CH = CH-C<u>H</u>a), 4.25 (dd, 1, J = 12.3 and 1.8, H-6′a), 4.22 (ddd, 1, J = 13.2, 5.1, and 1.5, Ar-CH = CH-C<u>H</u>b), 4.08 (dd, 1, J = 12.3 and 5.7, H-6′b), 3.84 (s, 3, OCH_3), 3.75 (ddd, 1, J = 9.6, 5.7 and 1.5, H-5′), 2.32 (s, 3, Ac), 1.24 (s, 9, Piv), 1.16 (s, 9, Piv), 1.15 (s, 9, Piv), 1.12 (s, 9, Piv), ^{13}C-NMR ($CDCl_3$); δ 177.7, 177.2, 176.5, 176.4 (C = O of Piv), 169.1 (C = O of Ac), 151.0 (C-3), 139.4 (C-4), 135.3 (C-1), 132.3 (Ar-<u>C</u>H = CH), 124.7 (Ar-CH = <u>C</u>H), 122.8 (C-5), 119.1 (C-6), 110.0 (C-2), 99.8 (C-1′), 72.3 (C-5′), 72.1 (C-3′), 71.0 (C-2′), 69.5 (Ar-CH = CH-<u>C</u>H_2), 67.9 (C-4′), 61.9 (C-6′), 55.7(-OCH_3), 38.8 × 2, 38.7 × 2 (C(= O)<u>C</u>$(CH_3)_3$), 27.1, 27.0 × 2 (C(= O)C(<u>C</u>$H_3)_3$), 20.7 (CH_3 of Ac).

(*E*)-3-(4-Acetoxy-3,5-dimethoxyphenyl)-2-propen-1-yl 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranoside (11b)

Reaction of compound 4 with compound 9b was done by method B to give compound 11b as colorless crystals in 90.1% yield; mp; 132–133°C, $[\alpha]_D^{24}$; −19.6°(c = 1.0, $CHCl_3$), ^{1}H-NMR ($CDCl_3$); δ 6.60 (broad s, 2, H-2, H-6), 6.51 (broad d, 1, J = 15.9, Ar-CH = CH), 6.14 (dt, 1, J = 15.9 and 5.7, Ar-CH = CH), 5.34 (t, 1, J = 9.6, H-3′), 5.14 (t, 1, J = 9.6, H-4′), 5.09 (dd, 1, J = 9.6 and 8.1, H-2′), 4.62 (d, 1, J = 8.1, H-1′), 4.50 (ddd, 1, J = 12.9, 5.1, and 1.5, Ar-CH = CH-CHa), 4.25 (dd, 1, J = 12.3 and 1.5, H-6′a), 4.22 (ddd, 1, J = 12.9, 5.1, and 1.5, Ar-CH = CH-CHb), 4.08 (dd, 1, J = 12.3 and 5.7, H-6′b), 3.83 (s, 6, OCH_3), 3.75 (ddd, 1, J = 9.6, 5.7, and 1.5, H-5′), 2.34 (s, 3, Ac), 1.24 (s, 9, Piv), 1.16 (s, 9, Piv), 1.15 (s, 9, Piv), 1.12 (s, 9, Piv), ^{13}C-NMR ($CDCl_3$): δ 178.1, 177.2, 176.5 × 2 (C = O of Piv), 168.8 (C = O of Ac), 152.1 (C-3, C-5), 134.8 (C-1), 132.6 (Ar-CH = CH), 128.3 (C-4), 124.8 (Ar-CH = CH), 103.0 × 2 (C-2, C-6), 99.9 (C-1′), 72.3 (C-5′), 72.1 (C-3′), 71.0 (C-2′), 69.5 (Ar-CH = CH-CH_2), 67.9 (C-4′), 61.9 (C-6′), 56.0 (-OCH_3), 38.7 × 4 (C(= O)C(CH_3)$_3$), 27.1, 27.0 × 2 (C(= O)C(CH_3)$_3$), 20.5 (CH_3 of Ac).

(*E*)-3-(4-Acetoxyphenyl)-2-propen-1-yl 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranoside (11c)

Reaction of compound 4 with compound 9c by method B provided compound 11c as colorless crystals in 90.8% yield; mp; 108–109°C, $[\alpha]_D^{24}$; −18.9°(c) (1.0, $CHCl_3$), ^{1}H-NMR ($CDCl_3$); δ 7.36 (broad d, 2, J = 8.7, H-2, H-6), 7.05 (broad d, 2, J = 8.7, H-3, H-5), 6.54 (broad d, 1, J = 15.9, Ar-CH = CH), 6.14 (dt, 1, J = 15.9 and 5.7, Ar-CH = CH), 5.33 (t, 1, J = 9.6, H-3′), 5.13 (t, 1, J = 9.6, H-4′), 5.08 (dd, 1, J = 9.6 and 8.1, H-2′), 4.61 (d, 1, J = 8.1, H-1′), 4.48 (dd, 1, J = 13.2 and 5.7, Ar-CH = CH-CHa), 4.23 (broad s, 1, H-6′a), 4.22 (dd, 1, J = 13.2 and 5.7, Ar-CH = CH-CHb), 4.07 (dd, 1, J = 12.0 and 5.7, H-6′b), 3.74 (ddd, 1, J = 9.6, 5.7, and 1.5, H-5′), 2.30 (s, 3, Ac), 1.24 (s, 9, Piv), 1.15 (s, 18, Piv), 1.13 (s, 9, Piv), ^{13}C-NMR ($CDCl_3$); δ178.1, 177.2, 176.5, 176.4 (C = O of Piv), 169.5 (C = O of Ac), 150.2 (C-4), 134.1 (C-1), 132.1 (Ar-CH = CH), 127.4 (C-2, C-6), 124.6 (Ar-CH = CH), 121.7 (C-3, C-5), 99.8 (C-1′), 72.3 (C-5′), 72.1 (C-3′), 71.0 (C-2′), 69.6 (Ar-CH = CH-CH_2), 67.9 (C-4′), 61.9 (C-6′), 38.8, 38.7 × 3 (C(= O)C(CH_3)$_3$), 27.1, 27.0 × 2 (C(= O)C(CH_3)$_3$), 21.1 (CH_3 of Ac).

(*E*)-3-(4-Hydroxy-3-methoxyphenyl)-2-propen-1-yl β-D-glucopyranoside ((*E*)-isoconiferin) (1a)

Compound 11a (3.14 g, 4.4 mM) was dissolved in MeOH (40 mL). NaOMe in MeOH (28%) (4.4 mL, 22 mM) was added slowly to the solution at 0°C.

The reaction solution was kept at r.t. for 4 h, neutralized with acetic acid, and evaporated *in vacuo* to give colorless residue. The residue was extracted with dioxane twice. The combined extracts were concentrated *in vacuo* to afford a crude product. The product was purified by silica gel column chromatography (eluent: $MeOH/CH_2Cl_2$ (1/5 (v/v))) to give compound 1a as deliquescent colorless crystals (1.35 g, 90.5% yield); $[\alpha]_D^{25}$; -47.7°(c = 1.0, CH_3OH), ^{1}H-NMR (CD_3OD); δ 7.01 (broad s, 1, H-2), 6.85 (broad d, 1, J = 8.4, H-6), 6.73 (d, 1, J = 8.1, H-5), 6.57 (broad d, 1, J = 15.6, Ar-C<u>H</u> = CH), 6.19 (dt, 1, J = 15.9 and 6.3, Ar-CH = C<u>H</u>), 4.50 (dd, 1, J = 12.3 and 6.3, Ar-CH = CH-C<u>H</u>a), 4.37 (d, 1, J = 7.5, H-1′), 4.29 (dd, 1, J = 12.3 and 6.3, Ar-CH = CH-C<u>H</u>b), 3.89 (dd, 1, J = 11.7 and 1.0, H-6′a), 3.85 (s, 3, OCH_3), 3.69 (dd, 1, J = 11.7 and 4.5, H-6′b), 3.42–3.27 (m, 3, H-3′, H-4′, H-5′), 3.24 (dd, 1, J = 8.4 and 7.5, H-2′), ^{13}C-NMR ($CDCl_3$); δ 149.0 (C-3), 147.6 (C-4), 134.3 (Ar-<u>C</u>H = CH), 130.1 (C-1), 123.6 (Ar-CH = <u>C</u>H), 121.1 (C-6), 116.1 (C-5), 110.4 (C-2), 103.0 (C-1′), 78.0 (C-3′), 77.9 (C-5′), 75.0 (C-2′), 71.6 (C-4′), 71.0 (Ar-CH = CH-<u>C</u>H_2), 62.7 (C-6′), 56.3 (OCH_3).

(*E*)-3-(4-Hydroxy-3,5-dimethoxyphenyl)-2-propen-1-yl β-D-glucopyranoside ((*E*)-isosyringin) (1b)

Compound 11b was deacylataed under the same conditions used with compound 11a to give compound 1b as an amorphous powder in 76.6% yield; $[\alpha]_D^{26}$; -28.9°(c = 1.0, CH_3OH), ^{1}H-NMR (CD_3OD); δ 6.71 (broad s, 2, J = 8.7, H-2, H-6), 6.58 (broad d, 1, J = 15.6, Ar-C<u>H</u> = CH), 6.23 (dt, 1, J = 15.9 and 6.2, Ar-CH = C<u>H</u>), 4.50 (ddd, 1, J = 12.1, 6.2, and 1.5, Ar-CH = CH-C<u>H</u>a), 4.37 (d, 1, J = 7.8, H-1′), 4.31 (ddd, 1, J = 12.1, 6.2, and 1.5, Ar-CH = CH-C<u>H</u>b), 3.89 (dd, 1, J = 12.0 and 1.5, H-6′a), 3.85 (s, 6, OCH_3), 3.69 (collapsed dd, 1, J = 12.0 and 5.4, H-6′b), 3.33 (t, 1, J = 9.0, H-3′), 3.31 (t, 1, J = 9.0, H-4′), 3.29 (ddd, 1, J = 9.0, 5.4, and 1.5, H-5′), 3.22 (dd, 1, J = 9.0 and 7.2, H-2′), ^{13}C-NMR ($CDCl_3$): δ 149.3 (C-3, C-5), 136.7 (C-4), 134.4 (Ar-<u>C</u>H = CH), 129.4 (C-1), 124.3 (Ar-CH = <u>C</u>H), 104.9 (C-2, C-6), 103.1 (C-1′), 78.1 (C-3′), 78.0 (C-5′), 75.1 (C-2′), 71.7 (C-4′), 70.9 (Ar-CH = CH-<u>C</u>H_2), 62.8 (C-6′), 56.7 (OCH_3).

(*E*)-3-(4-Hydroxyphenyl)-2-propen-1-yl β-D-glucopyranoside ((*E*)-triandrin) (1c)

The deacylation of compound 11c was carried out by the same method used with compound 11a to afford compound 1c as colorless crystals in 94.0% yield; mp; 176–178°C (lit. 178–180°C),[19] $[\alpha]_D^{23}$; (c = 1.0, CH_3OH), ^{1}H-NMR (CD_3OD); δ 7.25 (d, 2, J = 8.7, H-2, H-6), 6.72 (d, 2, J = 8.7, H-3 and H-5), 6.57 (broad d, 1, J = 16.2, Ar-C<u>H</u> = CH), 6.17 (dt, 1, J = 16.2 and 6.3, Ar-CH = C<u>H</u>), 4.49 (ddd, 1, J = 12.6, 5.7, and 1.2, Ar-CH = CH-C<u>H</u>a), 4.36 (d, 1, J = 7.8, H-1′), 4.28. (ddd, 1, J = 12.6, 5.7,

and 1.2, Ar-CH = CH-CHb), 3.88 (dd, 1, J = 12.0 and 1.5, H-6′a), 3.68 (collapsed dd, 1, J = 12.0 and 5.1, H-6′b), 3.40–3.20 (m, 2, H-3′, H-4′), 3.30 (ddd, 1, J = 9.0, 5.4, and 1.5, H-5′), 3.22 (dd, 1, J = 9.0 and 7.2, H-2′), ^{13}C-NMR ($CDCl_3$); δ 158.4 (C-4), 134.1 (Ar-CH = CH), 130.0 (C-1), 128.8 (C-3, C-5), 123.3 (Ar-CH = CH), 116.3 (C-2, C-6), 103.0 (C-1′), 78.1 (C-3′), 77.9 (C-5′), 75.1 (C-2′), 71.6 (C-4′), 71.0 (Ar-CH = CH-CH_2), 62.7 (C-6′).

RESULTS AND DISCUSSION

(*E*)-Isoconiferin (1a) has β-D-glucopyranose connected to the γ-position of (*E*)-coniferyl alcohol. It was obtained by reaction of (*E*)-coniferyl alcohol with D-glucosylating reagent. (*E*)-isosyringin (1b) and (*E*)-triandrin (1c) were obtained in a similar manner. Synthetic routes for compound 1a, 1b and 1c are shown in Figure 1.

Syntheses of Glycons 2, 3, and 4

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2), 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide (3) and trichloroacetoimidoyl 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyanoside (4) were prepared by conventional methods.[29–31]

Syntheses of Aglycons 9a, 9b, and 9c

There are several reports about the synthesis of compound 9a.[27,28,32] For example, Steglich and Zechlin described the synthesis of compound 9a from eugenol by four reaction steps; acetylation, epoxidation, bromination, and reduction with zinc powder.[32] However, the stereo-selectivity in the reduction was not high. The (*Z*)-isomer of compound 9a was also obtained with compound 9a; the E/Z ratio of the products was 88/12. The synthesis of compound 9a from vanillin (5a) by three reaction steps, namely, acetylation, Wittig reaction with (1,3-dioxolan-2-yl)methyltriphenylphosphonium bromide, and reduction with $NaBH_4$, was reported by Daubresse et al.[27] The E/Z ratio of the products after the reduction was approximately 70/30. Lu and Ralph reported the synthesis of compound 9a by the reduction with borane *tert*-butylamine complex of (*E*)-4-*O*-acetyl coniferyl aldehyde, which was obtained by acetylation of coniferyl aldehyde.[28] Coniferyl aldehyde is not easily available on large scale, although the yield of the reduction was excellent.

Fujiwara et al. reported the reduction of (*E*)-cinnamic acid to give (*E*)-cinnamic alcohol in 95% yield.[33] The chemoselective reduction of the

carboxylic acid to the corresponding alcohol was accomplished with $NaBH_4$ and *N,N*-dimethylchloromethylenium chloride, which was easily prepared from *N,N*-dimethylformamide (DMF) and oxalyl chloride, without reduction of olefin and ester.[33,34] We applied this method to the synthesis of compound 9a.

Compound 8a was prepared from vanillin (5a) in high yield by two synthetic routes, via acetyl vanillin (6a) or via ferulic acid (7a). Next, compound 8a was reduced with *N,N*-dimethylchloromethylenium chloride and $NaBH_4$. The results were shown in Table 1. The reduction of compound 8a was carried out under conditions similar to those reported by Fujiwara et al.[33] to give compound 9a in 47.2% yield (Entry 1). The yield of compound 9a increased to 63.1%, when using 2.0 eq of oxalyl chloride and 4.0 eq of $NaBH_4$ (Entry 3). However, this method was very tedious, because four anhydrous solvents had to be used. Anhydrous DMF and anhydrous CH_2Cl_2 were used for preparation of *N,N*-dimethylchloromethylenium chloride, and anhydrous CH_3CN and anhydrous THF were used for the reduction of the carboxylic compound. Because compound 8a and *N,N*-dimethylchloromethylenium chloride are both soluble, we used anhydrous DMF as the solvent and compound 9a was obtained in 80.2% yield (Entry 4). Compounds 9b and 9c were also obtained from the reduction of compounds 8b and 8c in 73.7% and 82.5% yields, respectively (Entry 5, 6).

Glycosylation

The results of glycosylation of compound 9a with compounds 2–4 are listed in Table 2. The Koenigs-Knorr reaction, which is a condensation of an

Table 1. Reduction of compounds 8a–8c

Entry	Starting material	(eq)	Solvents[a]	Oxalyl chloride (eq)	$NaBH_4$ (eq)	Yield (%)
1	8a	(1.0)	DMF, CH_2Cl_2, THF, CH_3CN	1.0	2.0	47.2
2	8a	(1.0)	DMF, CH_2Cl_2, THF, CH_3CN	1.5	4.0	54.0
3	8a	(1.0)	DMF, CH_2Cl_2, THF, CH_3CN	2.0	4.0	63.1
4	8a	(1.0)	DMF	2.0	4.0	80.2
5	8b	(1.0)	DMF	2.0	4.0	73.7
6	8c	(1.0)	DMF	2.0	4.0	82.5

[a]All solvents were anhydrous.

Table 2. Glycosylation of compounds 9a–9c with Compounds 2–4

Entry	Glycon	(eq)	Aglycon	(eq)	Catalyst	(eq)	Solvent[a]	Temperature (°C)	Time (h)	Yield (%)	Remarks
1	2	(2.5)	9a	(1.0)	$Hg(CN)_2$	(5.0)	CH_2ClCH_2Cl	50	15	21.1	
2	2	(2.5)	9a	(1.0)	$Hg(CN)_2 + Et_3N$	(5.0 + 2.5)	CH_2ClCH_2Cl	50	3	—	Orthoester 12a (91.5%)
3	3	(1.5)	9a	(1.0)	$Hg(CN)_2$	(1.6)	CH_2ClCH_2Cl	50	4.5	82.1	
4	3	(1.5)	9a	(1.0)	$AgClO_4$	(2.3)	CH_2Cl_2	−30	1.5	26.2	
5	3	(1.5)	9a	(1.0)	$AgSO_3CF_3$	(2.3)	CH_2Cl_2	−78	2	32.1	
6	3	(1.5)	9a	(1.0)	Ag_2SO_4	(2.3)	CH_2ClCH_2Cl	50	18	40.9	
7	4	(1.5)	9a	(1.0)	BF_3-Et_2O	(0.25)	CH_2Cl_2	−50	1.6	94.1	
8	4	(1.5)	9b	(1.0)	BF_3-Et_2O	(0.25)	CH_2Cl_2	−50	1.6	90.1	
9	4	(1.5)	9c	(1.0)	BF_3-Et_2O	(0.25)	CH_2Cl_2	−50	1.6	90.8	

[a]All solvents were anhydrous.

acylglycosyl halide with an alcohol, is widely used for the syntheses of β-glycosides. It is called the Helferich method when $Hg(CN)_2$ is used as the catalyst. It is known that the yields of β-glycosides by the Helferich method are often higher than those by the conventional Koenigs-Knorr method.[35] First, the glycosylation of compound 9a with compound 2 in the presence of $Hg(CN)_2$ was carried out. However, the yield of the expected β-glycoside 10a was only 21.1% (Entry 1). Wallace and Schroeder reported that $HgBrCN^-$, $HgBr_2$, HCN, HBr, and H^+ were presumably formed in the reaction of 2,3,4,6-tetra-*O*-methyl-α-D-glycopyranosyl bromide with cyclohexanol in the presence of $Hg(CN)_2$.[36] Such by-products may have an undesired influence on the glycosylation. We found that the reaction of compound 9a with compound 2 in the presence of Et_3N (as an acid acceptor) did not give the expected β-glycoside 10a, but gave the orthoester 12a (Figure 1) almost quantitatively (Entry 2). A classical glycosylation method is the orthoester method, which is an interconversion of an orthoester to a β-glycoside.[37] The conversion of orthoester 12a to β-glycoside 10a with an acid catalyst such as p-toluenesulfonic acid, BF_3-Et_2O, $AlCl_3$(anhydrous), and $ZnCl_2$ was tried. However, the yields of the expected glycoside 10a were low.

Second, compound 3 was used as the glycosylating agent instead of compound 2, because it was reported that the pivaloyl derivative was more reactive than the corresponding acetyl sugar and it was expected that the formation of orthoester was prevented by a steric hindrance of pivaloyl group at O-2 position.[29,38] As a result, it was found that the reaction of compound 9a (1.0 eq) with compound 3 (1.5 eq) in the presence of $Hg(CN)_2$ (1.6 eq) in anhydrous CH_2ClCH_2Cl at 50°C for 4.5 h gave the expected β-glycoside 11a in 82.1% yield (Entry 3).

Although the Helferich method gave a satisfactory result, it is unsuitable for large-scale preparation of compound 11a, because $Hg(CN)_2$ is a potentially harmful chemical. Another modification method of the Koenigs-Knorr method, using organic solvent soluble silver salts such as $AgClO_4$, $AgOSO_2CF_3$, was carried out (Entry 4, 5). But, the yield of compound 11a was low. The classical Koenigs-Knorr method using Ag_2SO_4 was also conducted, compound 11a was obtained in 40.9% yield (Entry 6).

We employed the imidate method for the preparations of β-glycosides. It is well-known that β-glycosides can be obtained from the corresponding α-imidates with good stereoselectivity in high yield.[39,40] Compound 4 was selected as the glycosylating agent. The reaction of compound 9a (1.0 eq) with compound 4 (1.5 eq) in the presence of BF_3-Et_2O (0.25 eq) in anhydrous CH_2Cl_2 at −50°C for 1.6 h gave the expected β-glycoside 11a in 94.1% yield (Entry 7).

The glycosylation of compounds 9b and 9c with compound 4 also gave the expected β-glycosides 11b and 11c in 90.1% and 90.8% yields, respectively (Entry 8, 9).

Deacylation

The protected β-glycoside 11a was treated with 28% NaOMe in MeOH at room temperature for 4 h to afford the free β-glycoside 1a in 90.5% yield. The ^{13}C-NMR spectrum of compound 1a obtained was in agreement with the data of (*E*)-isoconiferin, which was isolated from *Citrus unshu*.[5] It was found that compound 1a must be kept below 0°C in a refrigerator, because it decomposed spontaneously at room temperature.

Compounds 11b and 11c were easily converted by the same method used for compound 11a to provide compounds 1b and 1c in 76.6% and 94.0% yields, respectively. Our NMR data of compound 11b and 11c agreed with the data from *Pistia stratiotes*[14] and from *Salix acutifolia* bark,[19] respectively.

In summary, synthetic methods for the monolignol β-glycosides (*E*)-isoconiferin (1a), (*E*)-isosyringin (1b), and (*E*)-triandrin (1c) from compounds 5a, 5b and 5c have been established. These methods are applicable to large-scale preparations. The dehydrogenative polymerizations of monolignol β-glycosides will be reported in a subsequent article.

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