Total synthesis of (±)-divanillyltetrahydrofuran ferulate

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Abstract. A convenient method for the synthesis of sesquilignan *threo*- and *erythro*-(±)-divanillyltetrahydrofuran ferulate is described. The synthesis was based on a unified synthetic strategy involving two Stobbe condensations to give the skeleton of lignan, and then reduction reaction to form *meso*- and *threo*-(±)-secoisolanciresinol. *meso*- and *threo*-(±)-secoisolanciresinol were separated by flash column chromatography, followed by intramolecular reaction with TsCl to afford the key intermediate *meso*- or *threo*-(±)-shonanin, then condensation with ferulaic acid to obtain sesquilignan *threo*- or its analogue *erythro*-(±)-divanillyltetrahydrofuran ferulate.

Keywords. Synthesis; sesquilignan; stobbe reaction; divanillyltetrahydrofuran ferulate.

1. Introduction

Divanillyltetrahydrofuran ferulate was first isolated from the *Diospyros Kaki* calyces in 1985, and the natural plant was originally used both in Japanese folk medicine and in traditional Chinese medicine for the treatment of hiccup.¹ Divanillyltetrahydrofuran ferulate belong to the very interesting class of sesquilignan of natural lignan on account of their great number of structural possibilities. Sesquilignan family are widely occurring, and are found in all parts of producing plants, including the roots, stems, leaves, fruit, and seeds.² Recently, the identification of some sesquilignans was reported in various kinds of natural plants. Three sesquilignans *threo*-fuaiacylglycerol- β -O-4-syringaresinol ether, *threo*-fuaiacylglycerol- α -O-methyl- β -O-4-syringaresinol ether and *threo*-syringylglycerol- α -O-methyl- β -O-4-syringaresinol ether have been isolated for the first time.³ Two new sesquilignans were identified from a phytotoxic extract of *Brassica fruticulosa* L.⁴ Eight new tetrahydrofuran-type sesquilignans, bonaspectins A–H, as well as two new 8-O-4'-type sesquineolignans, neobonaspectins A and B, were isolated and characterized from the epigeal vegetative parts of *Bonamia spectabilis* (Choisy) HALL. F.⁵ Sesquilignans exhibit a wide range of biological activities, including antitumor, antioxidant and as pesticides.^{6–8} A recent report described the antiplas-

modial activity of sesquilignans against a chloroquine-resistant and a chloroquine-sensitive strain of plasmodium falciparum, the most dangerous human malaria parasite.⁹ Two sesquilignans Chushizisins H and I exhibited antioxidant activities against H₂O₂-induced impairment in PC12 cell.¹⁰ Although many sesquilignans have been found in plants and some showed potent biological activities, only a few have been synthesized. A paper has reported the synthesis of Haedoxan A, raw material starting from other known lignans of similar structure.¹¹ In Ichihara's synthesis of dehydrolappaol a dimethyl ether, various 2-alkyl-2-butenolactones were simply prepared from cyclopentadiene-maleic anhydride adducts through the retro-Diels-Alder reaction. The procedure was applied for the synthesis of dehydrolappaol A dimethyl ether.¹²

Here, we report the total syntheses of *threo*-(±)-divanillyltetrahydrofuran ferulate **1** and *erythro*-(±)-divanillyltetrahydrofuran ferulate **2**. The syntheses were based on a unified synthetic strategy involving Stobbe reaction to construct the skeleton of lignan (C₆–C₄–C₆) and resolution of *threo*- and *erythro*-isomers, followed by condensation with ferulaic acid to furnish the target product **1** and **2**.

As shown in scheme 1, cheaper Vanillin was used as raw materials, and the 4-hydroxyl group of vanillin was protected with benzyl chloride to afford the product **3**. Compound **3** underwent Stobbe condensation with diethyl succinate in the presence of sodium ethoxide in ethanol to produce compound **4**.

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Scheme 1.

Scheme 2.

Scheme 3.

The *trans*-(*E*)-configuration of the olefinic double bond was evident from the appearance of the deshielded vinylic proton at δ 7.87 in its ^1H NMR spectrum. Compound **4** was methylated with diazomethane in methanol to yield the diester **5**. The second Stobbe condensation of **5** with **3** in methanol in the presence of sodium methoxide yielded compound **6**. The deshielded vinylic proton at δ 7.96 in the ^1H NMR spectrum of **6** indicated the *trans*-(*E*)-configuration for both the olefinic double bonds.^{13–15} Compound **6** was again methylated to produce a diester **7**. Treatment of **7** with $\text{LiAlH}_4/\text{AlCl}_3$ afforded the unsaturated diol **8**, followed by hydrogenation with a 10% palladium on charcoal catalyst to pro-

duce a readily separable mixture (approximate 1 : 1) of diols *meso*-**9a** and *threo*-($\pm$)-**9b**. *Threo*-($\pm$)-**9b** had consistently larger R_f values than those of the corresponding *meso*-**9a**, and each pair was easily separated by flash column chromatography over silica gel. The configuration of *threo*-($\pm$)-**9b** was in agreement with those reported in the literatures.^{16,17}

The 4-hydroxyl group of *meso*-secoisolangiresinol **9a** or *threo*-($\pm$)-secoisolangiresinol **9b** was protected with benzyl chloride to afford the compound *meso*-**10a** or *threo*-($\pm$)-**10b**. Reaction of diol *meso*-**10a** or *threo*-($\pm$)-**10b** with equimolar TsCl in pyridine under dilution at room temperature gave the corresponding tetrahydrofuran *meso*-**11a** or *threo*-($\pm$)-

Scheme 4.

11b, which were hydrogenated with 10% palladium on charcoal catalyst to obtain the key intermediate *meso*-shonanin **12a** and *threo*-(±)-shonanin **12b**, respectively (scheme 2).^{17–19}

Ferulaic acid was esterified with MeOH, followed by protection with MOMCl to produce the compound **13**. Hydrolysis of the ester **13** gave the intermediate **14** (scheme 3).

As shown in scheme 4, the condensation of the intermediate *meso*-**12a** with the acid **14** employing DCC and DMAP, followed by deprotection of MOM group using HCl at room temperature furnished the target product *erythro*-(±)-**2**. Following the procedure described for the preparation of *erythro*-(±)-**2**, and starting with *threo*-(±)-**12b**, compound *threo*-(±)-**1** was obtained. The spectral data of *threo*-(±)-**1** were in agreement with those found in the literature.^{1,20}

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- meso*-Shonanin **12a**: IR (KBr/cm⁻¹): 3339, 2916, 1609, 1520, 1253, 1038, 928. ¹H NMR (CDCl₃, 500 MHz) δ: 2.44–2.50 (*m*, 4H, 2 × ArCH₂CH), 2.78–2.85 (*m*, 2H, 2 × ArCH₂CH), 3.61 (*dd*, 2H, *J* = 8.0, 4.5 Hz, CH₂O), 3.75 (*dd*, 2H, *J* = 8.0, 6.0 Hz, CH₂O), 3.82 (*s*, 6H, 2 × OCH₃), 6.50–6.82 (*m*, 6H, ArH). ¹³C NMR (CDCl₃, 125 MHz) δ: 33.2 (C-7', C-7''), 43.8 (C-3, C-4), 55.9 (2 × OCH₃), 72.3 (C-2, C-5), 111.2 (C-2', C-2''), 114.4 (C-5', C-5''), 121.3 (C-6', C-6''), 132.5 (C-1', C-1''), 143.9 (C-4', C-4''), 146.5 (C-3', C-3''). HRMS calcd for C₂₀H₂₈NO₅ (M + NH₄⁺): 362.1962; found: 362.1959. *threo*-(±)-Shonanin **12b**: IR (KBr/cm⁻¹): 3403, 2918, 1604, 1515, 1261, 1042. ¹H NMR (CDCl₃, 500 MHz) δ: 2.11–2.18 (*m*, 2H, 2 × ArCH₂CH), 2.51–2.61 (*m*, 4H, 2 × ArCH₂CH), 3.53 (*dd*, 2H, *J* = 9.0, 5.5 Hz, CH₂O), 3.82 (*s*, 6H, 2 × OCH₃), 3.92 (*dd*, 2H, *J* = 9.0, 6.5 Hz, CH₂O), 6.51–6.90 (*m*, 6H, ArH). ¹³C NMR (CDCl₃, 125 MHz) δ: 39.2 (C-7', C-7''), 46.5 (C-3, C-4), 55.8 (2 × OCH₃), 73.3 (C-2, C-5), 111.1 (C-2', C-2''), 114.1 (C-5', C-5''), 121.3 (C-6', C-6''), 132.3 (C-1', C-1''), 143.9 (C-4', C-4''), 146.4 (C-3', C-3''). HRMS calcd for C₂₀H₂₈NO₅ (M + NH₄⁺): 362.1962; found: 362.1964.
- erythro*-(±)-Divanillyltetrahydrofuran ferulate **2**: IR (KBr/cm⁻¹): 3410, 2935, 1710, 1612, 1523, 1245, 1236, 928. ¹H NMR (DMSO-*d*₆, 500 MHz) δ: 2.45–

2.55 (*m*, 4H, $2 \times \text{ArCH}_2\text{CH}$), 2.73–2.82 (*m*, 2H, $2 \times \text{ArCH}_2\text{CH}$), 3.78 (*s*, 3H, OCH_3), 3.83 (*s*, 3H, OCH_3), 3.86 (*s*, 3H, OCH_3), 3.98 (*dd*, 2H, $J = 8.0$, 6.0 Hz, CH_2O), 4.16 (*dd*, 2H, $J = 8.0$, 5.5 Hz, CH_2O), 6.55 (*d*, 1H, $J = 16.0$ Hz, $\text{CH}=\text{CHCO}$), 6.61–7.38 (*m*, 9H, ArH), 7.67 (*d*, 1H, $J = 16.0$ Hz, $\text{CH}=\text{CHCO}$). ^{13}C NMR ($\text{DMSO}-d_6$, 125 MHz) δ : 31.6 (C-7', C-7''), 41.2 (C-4, C-3), 54.2 (OCH_3), 55.7 (OCH_3), 55.9 (OCH_3), 62.5 (C-2), 62.7 (C-5), 111.0, 111.8, 112.1, 114.5 (ArCH=CH), 115.4, 115.5, 120.6, 121.1, 121.7, 123.0, 125.5, 130.2, 130.7, 144.6, 145.3 (ArCH=CH), 145.7, 147.3, 147.8, 149.3, 150.1, 165.5 (C=O). HRMS calcd for $\text{C}_{30}\text{H}_{36}\text{NO}_8$ ($\text{M} + \text{NH}_4^+$): 538.2436; found: 538.2441. *threo*-($\pm$)-Divanillyltetrahydrofuran ferulate 1: m.p. 174–176°C. IR ($\text{KBr}/\text{cm}^{-1}$): 3390,

2935, 1700, 1620, 1520, 1240, 1216, 928. ^1H NMR ($\text{DMSO}-d_6$, 500 MHz) δ : 2.12–2.16 (*m*, 2H, $2 \times \text{ArCH}_2\text{CH}$), 2.73–2.76 (*m*, 4H, $2 \times \text{ArCH}_2\text{CH}$), 3.72 (*s*, 3H, OCH_3), 3.84 (*s*, 6H, $2 \times \text{OCH}_3$), 3.94 (*dd*, 2H, $J = 9.0$, 5.5 Hz, CH_2O), 4.28 (*dd*, 2H, $J = 9.0$, 6.0 Hz, CH_2O), 6.53 (*d*, 1H, $J = 16.0$ Hz, $\text{CH}=\text{CHCO}$), 6.60–7.45 (*m*, 9H, ArH), 7.62 (*d*, 1H, $J = 16.0$ Hz, $\text{CH}=\text{CHCO}$). ^{13}C NMR ($\text{DMSO}-d_6$, 125 MHz) δ : 33.6 (C-7', C-7''), 39.0 (C-3), 39.5 (C-4), 55.3 (OCH_3), 55.6 (OCH_3), 56.0 (OCH_3), 64.0 (C-2), 64.2 (C-5), 111.2, 111.8, 112.7, 114.8 (ArCH=CH), 115.0, 115.4, 121.2, 121.5, 122.0, 123.3, 125.7, 130.4, 130.7, 143.8, 144.1, 144.3, 145.0 (ArCH=CH), 147.2, 147.5, 149.1, 166.9 (C=O). HRMS calcd for $\text{C}_{30}\text{H}_{36}\text{NO}_8$ ($\text{M} + \text{NH}_4^+$): 538.2436; found: 538.2440.