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First Total Synthesis of 1,4-Benzodioxane Lignans Cadensin G

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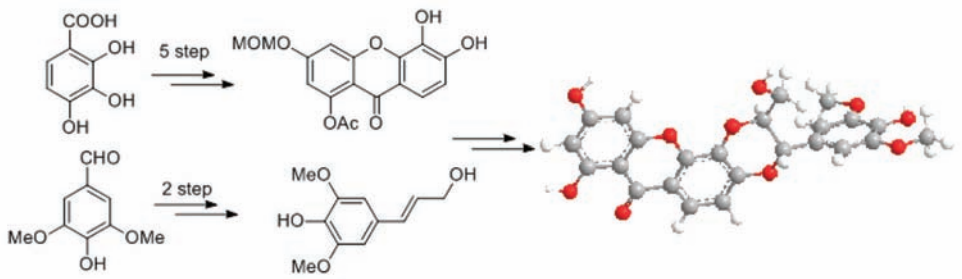
ABSTRACT Cadensin G, 1,4-Benzodioxane lignans isolated from *Psorospermum febrifugum*, has excellent antitumor activity. In this paper, we report the first total synthesis of Cadensin G, using selective protection of 1,3,5,6-tetrahydroxyxanthone phenolic hydroxyl groups and biomimetic coupling as critical steps. Under the action of potassium ferricyanide, the coupling of sinapyl alcohol and phenolic hydroxyl group protected 1,3,5,6-tetrahydroxyxanthone afforded Cadensin G.



KEYWORDS 1,4-Benzodioxane lignans, Cadensin G, Oxidative coupling, Selective protection.

INTRODUCTION

1,4-Benzodioxane lignans are a class of neolignans whose C-7 and C-8 of one C_6C_3 unit, respectively, formed by linking oxygen atoms with C-3' and C-4' of another C_6C_3 unit. At present, it has been found to be concentrated in plant callus and priming cells.[1] Due to its wide range of physiological activities, such as liver protection,[2] antioxidation,[3] antitumor,[4] and insecticidal activity,[5] it has attracted wide interests from chemical synthesis researchers. Studies have shown that the core structure of 1,4-benzodioxane contributes to the important physiological activity of 1,4-benzodioxane lignans.

Cadensin G [**1**, **Figure 1]**, the 1,4-benzodioxane lignans, was first extracted from *Psorospermum febrifugum* by Monamed Abou-shore, in 1989.[6] In 2009, Naonobu Tanaka *et al*.[7] systematically evaluated the cytotoxicity of cadensin G on human tumor cells. Studies have shown that cadensin G has moderate cytotoxicity against KB (human epidermoid carcinoma of nasopharynx), K_{562} (leukemia), MCF_7 (breast carcinoma), and $COLO_{205}$ (colon carcinoma) cell lines, as well as multidrug-resistant human cancer cell lines including KBC_2 (colchicine-resistant KB) and K_{562}/Adr (doxorubicin-resistant K_{562}) cells.

Here, we report the first total synthesis of cadensin G involving synthesis of 1,4-benzodioxane nucleus by oxidative coupling of potassium ferricyanide based on a biomimetic coupling strategy. The phenolic hydroxyl group is then deprotected to achieve total synthesis of the natural compound cadensin G. Furthermore, the 1,3,5,6-tetrahydroxyxanthone protection, deprotection method, and biomimetic coupling reaction conditions are described in this paper.

RESULTS AND DISCUSSION

Through our retrosynthetic analysis of **1** depicted in **Scheme 1**, the target compound **1** could be made from sinapyl alcohol and 1,3,5,6-tetrahydroxyxanthone using

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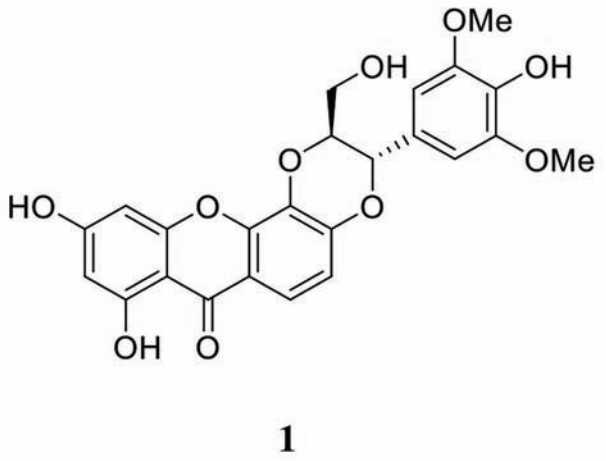
oxidative coupling reaction. Since the coupling reaction under the oxidation of potassium ferricyanide is a free radical reaction, the *m*-dihydroxy of 1,3,5,6-tetrahydroxyxanthone is susceptible to give side reactions, so the protection of the phenolic hydroxyl group is required before the oxidation coupling reaction. 1,3,5,6-tetrahydroxyxanthone can be synthesized with phloroglucinol and 2,3,4-trihydroxybenzoic acid.[8] The reduction of (E)-ethyl 3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoate with lithium aluminum hydride affords sinapyl alcohol. (E)- Ethyl 3- (4-hydroxy-3,5-dimethoxyphenyl) prop-2-enoate could be easily obtained from syringaldehyde and monoethyl malonate by the Knoevenagel condensation reaction.[9]

As shown in **Scheme 2**, (E)-ethyl 3-(4-hydroxy-3,5-dimethoxyphenyl) prop-2-enoate **3** was easily prepared by a Knoevenagel condensation of syringaldehyde and monoethyl malonate using pyridine as a solvent and piperidine as a catalyst in a yield of 97%.[10] Then, **3** was reduced by lithium aluminum hydride to realize the synthesis of sinapyl alcohol **4** in a yield of 77%.[11] In **Scheme 3**, we described in detail the preparation of phenolic hydroxyl groups in 1,3,5,6-tetrahydroxyxanthone. First, phloroglucinol reacted with 2,3,4-trihydroxybenzoic acid to form 1,3,5,6-tetrahydroxyxanthone **7** using phosphorus oxychloride.[12] The product **8** was obtained by Williamson reaction with dichlorodiphenylmethane and o-diphenol **7**. Two phenolic hydroxyls were separately protected to afford an intermediate product **10**, one of which was protected by chloromethyl methyl ether to form an acetal, the other reacted with acetic anhydride to give an ester. Then, the protecting group of the o-dihydroxy was removed by 10% Pd/C to obtain the product **11** in a yield of 91%.[13] Finally, compound **11** was coupled with compound **4** under the action of potassium ferricyanide to obtain the final product cadensin G (**1**). The plausible mechanism for the formation of **1** has been outlined in **Scheme 4**.[14]

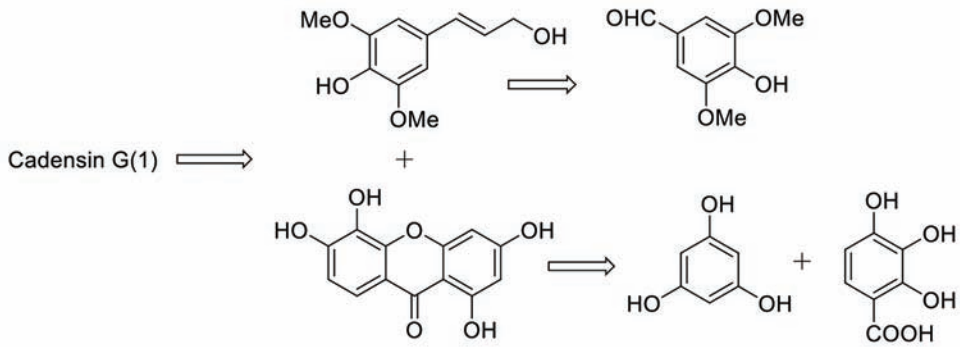


1

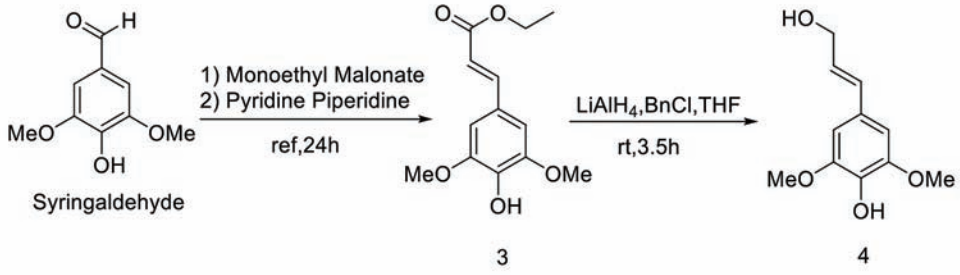
Figure 1: Cadensin G (1)

EXPERIMENTAL SECTION

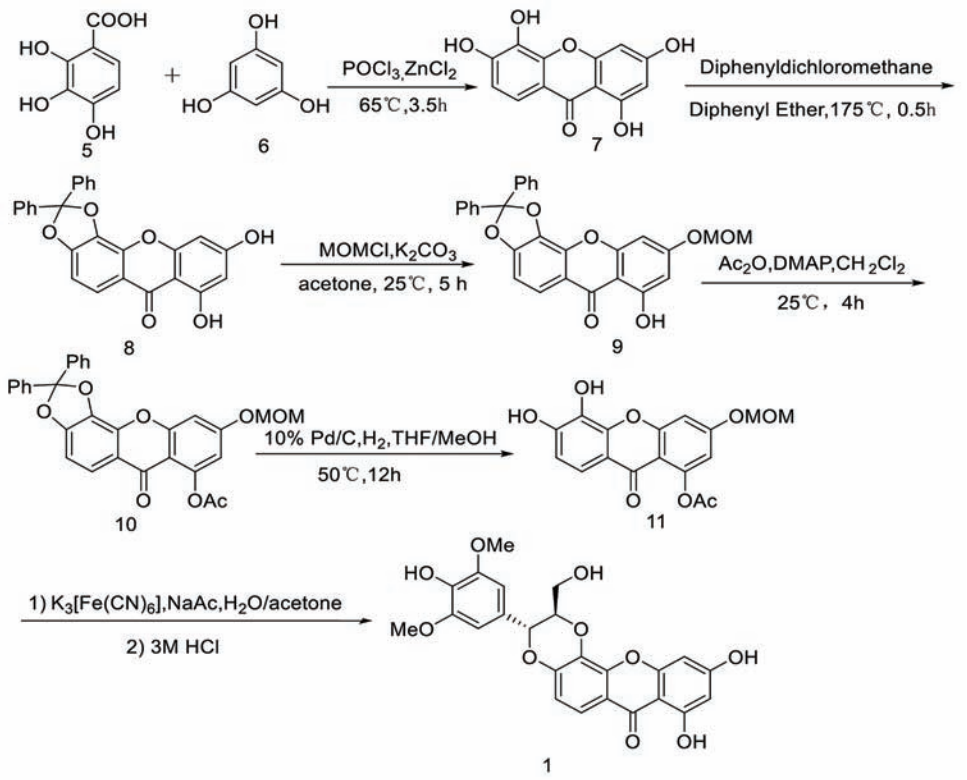
All solvents and reagents used in this study were commercially available AR grade and no further purification was required. The progress of the reaction was monitored by thin-layer chromatography on a silica gel plate of GF_{254}, and the product was separated and purified by column chromatography using silica gel (200–300 mesh). Melting points were determined on uncalibrated Gallenkamp melting point apparatus. The ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra were recorded on a Bruker AM-500 MHz spectrometer. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII47e spectrometer.



Scheme 1: Retrosynthetic analysis for preparation of 1



Scheme 2: Synthesis of sinapyl alcohol (4)



Scheme 3: Synthesis of cadensin G (1)

(E)-ethyl 3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoate (3)

The syringaldehyde (21.00 g, 0.115 mol), monoethyl malonate (22.83 g, 0.173 mol), and piperidine (1.78 g, 0.021 mol) were dissolved in pyridine (40 mL) and refluxed at 100°C for 24 h. After cooling to room temperature, the reaction mixture was added to ice cooled hydrochloric acid to neutralize the pyridine, and the mixture was slowly poured into deionized water. The product **3** was isolated by filtration as white solid:[15] m.p. 75–77°C (lit. 76–78°C); yield: 27.87 g (96%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.34 t (3H, CH_2CH_3, *J* = 7.0 Hz), 3.92 s (6H, 2 × OCH_3); 4.26 q (2H, CH_2CH_3, *J* = 12.0 Hz), 6.31 d (1H, ArCH=C*H*, *J* = 15.5 Hz), 6.78 s (2H, 2 × ArH), 7.60 d (1H, ArC*H*=CH, *J* = 16.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.4, 56.3 ($ArOCH_3$), 60.4 (OCH_2), 105.1, 115.9 (ArCH = *C*H), 125.9, 137.3, 145.0 (Ar*C*H = CH), 147.3, 167.3 (C=O).

(E)-sinapyl alcohol (4)

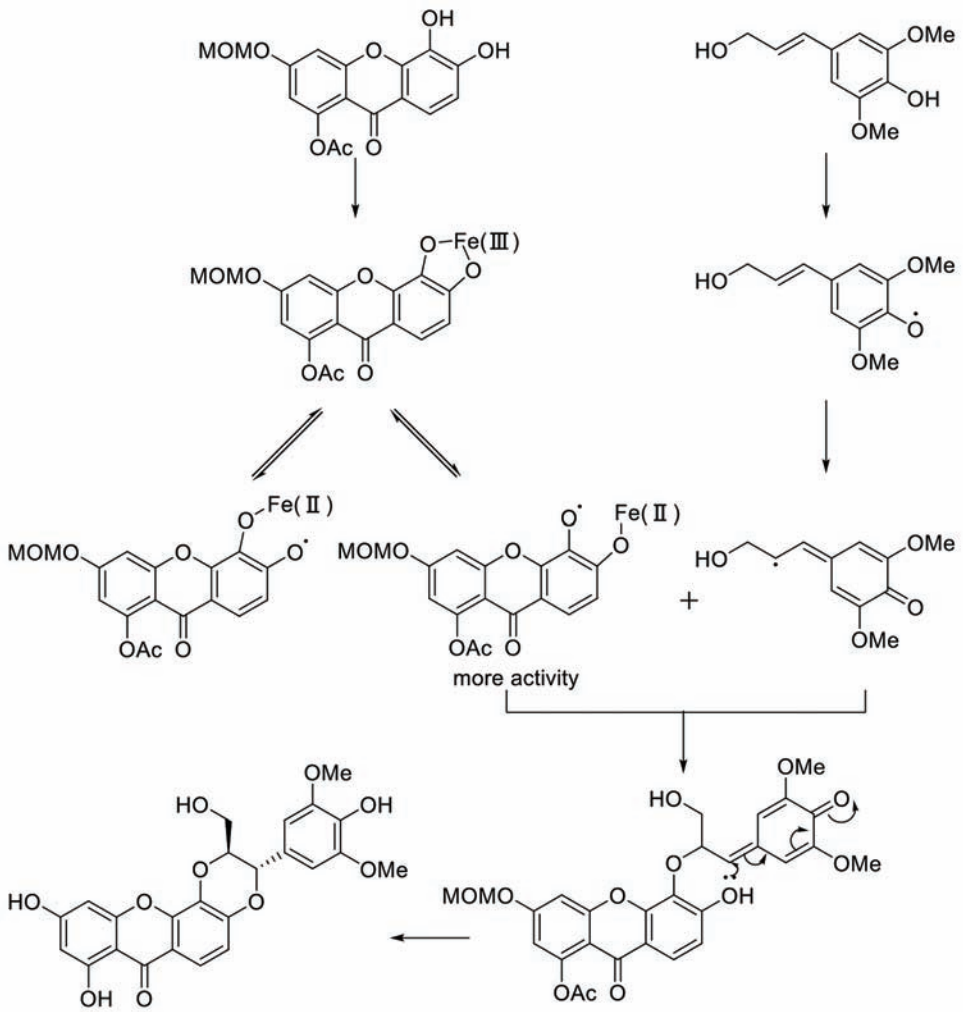
The tetrahydrofuran (THF) solvent treated without water was used in this step. Under anhydrous anoxic and ice bath conditions, 20% (v/v=13.6:54.4) benzyl chloride in THF was added dropwise to the suspension of $LiAlH_4$ (6.90 g, 0.182 mol) in THF. Next, the mixture was stirred at 25°C for 1 h, followed by further reaction for 1.5 h, a solution of compound **3** (15.00 g, 0.060 mol) in THF was added thereto. And then quenched with saturated ammonium chloride solution (20 ml) under ice bath, the mixture was extracted with diethyl ether (3×100 ml). After the solvent being removed by vacuum evaporation, the product **4** was purified by silica gel column chromatography (petroleum ether/EtOAc = 2:1) as yellowish solid:[16] m.p. 62–64°C (lit. 61–65°C); yield: 10.02 g (80%); ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.90 s (6H, 2 × OCH_3), 4.31 dd (2H, CHC*H*$_2$OH, J = 6.0 Hz, *J* = 1.5 Hz), 5.65 s (1H, ArOH), 6.24 dt (1H, ArCH=C*H*CH$_2$, *J* = 15.5 Hz, *J* = 6.0 Hz), 6.52 d (1H, ArC*H*=CH, *J* = 16.0 Hz), 6.63 s (2H, 2 × ArH); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 56.3 ($ArOCH_3$), 63.8 (CH_2OH), 103.4, 126.8 (ArCH = *C*H), 128.4, 131.6 (Ar*C*H = CH), 135.0, 147.0.

1,3,5,6-tetrahydroxyxanthone(7)

Pyrogallol (6.00 g, 0.048 mol), 2,3,4-trihydroxybenzoic acid (8.10 g, 0.048 mol), $ZnCl_2$ (42.00 g, 0.300 mol), and $POCl_3$ (90 mL) were added to a round-bottom flask under anhydrous oxygen-free nitrogen atmosphere. After reacting at 65°C for 3.5 h, the reaction solution was cooled to room temperature, poured into ice water (400 mL), and filtered. Then, the filter cake was washed with distilled water to neutral and then dried to obtain a yellow solid compound **7**:[17] m.p. >300°C (lit. >300°C); yield: 8.98 g (72%); ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 6.14 d (1H, *J* = 1.5 Hz, ArH), 6.38 d (1H, ArH, *J* = 2.0 Hz), 6.90 d (1H, ArH, *J* = 9.0 Hz), 7.48 d (1H, ArH, *J* = 9.0 Hz), 9.41 s (1H, ArOH), 10.51 s (1H, ArOH), 10.90 s (1H, ArOH), 13.10 s (1H, ArOH); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 93.9, 98.2, 102.3, 113.2, 115.9, 132.4, 146.0, 151.8, 157.3, 162.8, 165.1, 179.6 (C=O).

7,9-Dihydroxy-2,2-diphenyl-6*H*-[1,3]dioxolo[4,5-c] xanthen-6-one (8)

Compound **7** (8.00 g, 0.030 mol) and dichlorodiphenylmethane (11.08 g, 0.046 mol) were added to diphenyl ether (200 mL). The reaction mixture was heated



Scheme 4: Plausible mechanism for the formation of 1

to 175°C under N_2 atmosphere for 0.5 h. Cooling to room temperature, the reaction mixture was poured into petroleum ether (600 mL). The product **8** was isolated by filtration and purified by silica gel column chromatography (petroleum ether/EtOAc = 8:1) as light yellow solid:[13] m.p. 211–213°C (lit. 212–214°C); yield: 11.08 g (85%); ^{1}H-NMR (500 MHz, DMSO-d_6): δ 6.19 d (1H, ArH, *J* = 2.0 Hz), 6.41 d (1H, ArH, *J* =1.5 Hz), 7.20 d (1H, ArH, *J* = 8.5 Hz), 7.46–7.48 m (6H, 6 × ArH), 7.57–7.59 m (4H, 4 × ArH), 7.74 d (1H, ArH, *J* = 8.5 Hz), 12.88 s (1H, ArOH); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 93.7, 98.5, 101.9, 106.9, 112.5, 114.8 (OCO), 115.7, 126.0, 128.2 (Ar), 132.4, 137.2, 146.1, 152.1, 158.0, 162.0, 169.3, 179.0 (C=O).

7-Hydroxy-9-(methoxymethoxy)-2,2-diphenyl-6*H*-[1,3]dioxolo[4,5-c]xanthen-6-one (9)

K_2CO_3 (6,48 g, 0.048 mol) was added to a solution of compound **8 (**10.00 g, 0.024 mol) in acetone (200 mL). Then followed by stirring for 0.5 h, MOMCl (2.70 mL, 0.036 mol) was added. The reaction mixture was stirred for 6 h and poured into H_2O (300 mL). The precipitate was collected by filtration and washed with water (10 mL × 3). The compound **9** was purified by silica gel column chromatography (petroleum ether/EtOAc = 8:1) as white solid:[18] m.p. 125–126°C (lit. 125–127°C); yield: 9.98 g (91%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.51 s (3H, OCH_3), 5.26 s (2H, OCH_2O), 6.46 d (1H, ArH, *J* = 1.5 Hz), 6.67 d (1H, ArH, *J* = 2.0 Hz), 6.99 d (1H, ArH, *J* = 8.5 Hz), 7.42–7.43 m (6H, 6 × ArH), 7.64–7.65 m (4H, 4 × ArH), 7.87 d (1H, ArH, *J* = 8.5 Hz), 12.92 s (1H, ArOH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 56.7 (OCH_3), 94.5, 97.3, 98.0 (OCH_2O), 105.2, 107.7, 113.8 (OCO), 116.5, 120.4, 125.5, 128.3, 128.7 (Ar), 134.5, 138.5, 141.3, 151.6, 157.1, 161.2, 165.1, 180.2 (C=O).

8-(Methoxymethoxy)-6-oxo-2,2-diphenyl-6*H*-[1,3] dioxolo[4,5-c]xanthen-7-yl acetate (10)

Compound **9** (8.00 g, 0.017 mol), Ac_2O (2.27 g, 0.022 mol), and DMAP (3.13 g, 0.003 mol) were added into dichloromethane (200 mL). After stirring at room temperature for 0.5 h, dichloromethane (200 mL) was added to dilute the reaction mixture. The organic phase was washed with H_2O (200 mL × 3) and evaporated in vacuum. The compound **10** was purified by silica gel column chromatography (petroleum ether/EtOAc = 4:1) as white solid:[19] m.p. 191–193°C (lit. 192–193°C); 8.03 g (93%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.47 s (3H, $OCOCH_3$), 3.52 s (3H, OCH_3), 5.28 s (2H, OCH_2O), 6.68 d (1H, ArH, *J* = 2.0 Hz), 6.95 d (1H, ArH, *J* = 8.5 Hz), 7.10 d (1H, ArH, *J* = 2.0 Hz), 7.41–7.42 m

(6H, 6 × ArH), 7.63–7.64 m (4H, 4 × ArH), 7.84 d (1H, ArH, *J* = 8.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 21.2 ($CO\mathit{C}H_3$), 55.4 (OCH_3), 96.7 (OCH_2O), 101.4, 104.5, 112.7 (OCO), 121.2, 126.5 (Ar), 134.6, 142.6, 151.5, 154.1, 157.5, 163.7, 170.3 ($COCH_3$), 176.4 (C=O). Mass spectrum (HRMS), m/z: 511.1319 $[M + H]^+$ (for $C_{30}H_{22}O_8$ calculated: 510.1315).

5,6-Dihydroxy-3-(methoxymethoxy)-9-oxo-9*H*-xanthen-1-yl acetate (11)

Under H_2 atmosphere, 10% Pd/C (0.60 g) was suspended in a solution of compound **10 (**6.0 g, 0.012 mol) in THF/MeOH (50 mL/50 mL). After stirring at 50°C for 3 h, the reaction mixture was filtered to remove Pd/C. The solvent was removed *in vacuo* and the residue was washed with petroleum ether/EtOAc (50 mL/10 mL). The product **11** was isolated by filtration as white solid:[19] m.p. 150–152°C (lit. 149–151°C); 3.7 g (91%). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.49 s (3H, $OCOCH_3$), 3.43 s (3H, OCH_3), 5.37 s (2H, OCH_2O), 6.78 d (1H, ArH, *J* = 1.5 Hz), 6.88 d (1H, ArH, *J* = 9.0 Hz), 7.11 d (1H, ArH, *J* = 1.5 Hz), 7.43 d (1H, ArH, *J* = 9.0 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 21.3 ($CO\mathit{C}H_3$), 56.7 (OCH_3), 95.3 (OCH_2O), 100.9, 102.2, 108.9, 117.6, 133.1, 146.2, 151.5, 152.2, 162.4, 169.6 ($\mathit{C}OCH_3$), 174.9 (C=O).

Cadensin G (1)

Sinapyl alcohol (1.05 g, 0.005 mol), compound **11 (**1.73 g, 0.005 mol), potassium ferricyanide solution (3.29 g, 0.010 mol in 50 mL of H_2O), and sodium acetate solution (2.45 g, 0.003 mmol, in 50 mL of H_2O) were added sequentially to acetone/H_2O = 1:1 (200 mL). After stirring at room temperature for 3 d, the reaction solution was filtered and then concentrated *in vacuo*. Next, acetone (50 mL) and 3 M HCl were added thereto and stirred at 40°C for 6 h. The mixture was extracted with dichloromethane and the organic phase was evaporated *in vacuo*. The product **1** was isolated and purified by reverse-phase silica gel column as white solid: m.p. 264–266°C (lit. 265–266°C); 0.42 g (18%). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.51 dd (1H, $CHC\mathit{H}_2OH$, *J* = 12.5 Hz, J = 4.5 Hz), 3.69 m (1H, $CHC\mathit{H}_2OH$), 3.77 s (6H, 2 × $ArOCH_3$), 4.33 m (1H, $ArCHC\mathit{H}CH_2$), 5.08 d (1H, $ArC\mathit{H}CH$, *J* =7.5 Hz), 5.75 d (1H, ArH, *J* = 1.5 Hz), 5.93 d (1H, ArH, *J* = 1.0 Hz), 6.77 s (2H, 2 × ArH), 6.95 d (1H, ArH, *J* = 8.5 Hz), 7.53 d (1H, ArH, *J* = 8.5 Hz). ^{13}C-NMR (125 MHz, DMSO-d_6): δ 56.6 (OCH_3), 60.3 ($CH\mathit{C}H_2OH$), 74.3 (ArCHOAr), 77.3 (ArCHCHOAr), 94.6, 98.6, 102.2, 106.0, 114.2, 117.2, 126.1, 130.1, 132.0, 136.8, 148.5, 149.5, 157.6, 163.4, 166.0, 179.7 (C=O). Mass spectrum (HRMS), m/z: 469.1062 $[M + H]^+$. (lit. ^{1}H-NMR (470 MHz, DMSO-d_6): δ 3.42 dd (1H, $CHC\mathit{H}_2OH$, *J* = 12.4 Hz, *J* = 4.3 Hz), 3.67 m (1H, $CHC\mathit{H}_2OH$), 3.74 s (6H, 2 × $ArOCH_3$), 4.35 m (1H, $ArCHC\mathit{H}CH_2$), 5.10 d (1H, $ArC\mathit{H}CH$, *J* =7.8 Hz), 6.19 d (1H, ArH, *J* = 1.1 Hz), 6.38 d (1H, ArH, *J* = 1.1 Hz), 6.77 s (2H, 2 × ArH), 7.05 d (1H, ArH, *J* = 8.5 Hz), 7.61,d (1H, ArH, *J* = 8.5 Hz). Mass spectrum (HRMS), m/z: 469.1062 $[M + H]^+$).[6]

CONCLUSION

We achieved the first total synthesis of natural 1,4-benzodioxane lignans cadensin G using a 8-step reaction. Intermediate **4** was synthesized in 77% yield using syringaldehyde as a precursor, and intermediate **11** was obtained in 47% yield using phloroglucinol and 2,3,4-trihydroxybenzoic acid as precursors. Selective protective synthesis of 1,3,5,6-tetrahydroxyxanthone fragment and ring forming of 1,4-benzodioxane nucleus under oxidative coupling reaction of potassium ferricyanide were a key step in this reaction. We are continuing to study the bioactivity of cadensin G and the synthesis of related derivatives.

ACKNOWLEDGMENT

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