**Research Article**

**Synthesis of Magnolignan, a New Pigment Lightening Component, via a Suzuki-Miyaura Reaction**

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Magnolignan, 2,2'-dihydroxy-5,5'-dipropyl-biphenyl (1), is a down-regulator of melanin synthesis that inhibits the maturation of tyrosinase. In this study, a concise total synthesis of 1 was achieved in five steps with 50% overall yield starting from commercially available *trans*-anethole (2) via a Suzuki-Miyaura reaction.

### 1. Introduction

Various treatments with melanin synthesis inhibitors, lasers, and chemical peels have been investigated to achieve lightening effects for pigmented skin in the field of cosmetics. In particular, melanin synthesis inhibitors, such as hydroquinone, have been shown to be an effective treatment of melasma and a prophylactic agent for hyperpigmentation [1]. Melanin synthesis inhibitors have been widely used as lightening components in cosmetic formulations. While hydroquinone has a remarkable lightening effect, its strong bleaching action causes skin irritation. Therefore, alternative hydroquinone derivatives that have a mild or nonirritating effect have been investigated.

Researchers at Kanebo Cosmetics Co. Ltd., Japan, have proved that compounds with a biphenol framework are extraordinarily effective as melanin synthesis inhibitors [2]. Structure-activity relationship (SAR) studies of biphenol compounds strongly suggested that 2,2'-dihydroxy-5,5'-dipropyl-biphenyl (1, Figure 1), also known as magnolignan or tetrahydro magnolol, has a greater lightening effect than the natural products magnolol and honokiol, which are isolated from the bark of *Magnolia officinalis* or *M. obovata* [3]. The lightening effect of magnolignan 1 was validated by several bioassays, such as the de novo melanin synthesis [4], the tyrosine hydroxylase assay [5], and melanin measurements [6]. For these studies, the new lightening compound 1 was synthesized using the oxidative coupling method previously reported by Sartori and co-workers [7]. Here, in this paper, a concise total synthesis of magnolignan 1 is described. The key step in the synthesis is a Suzuki-Miyaura reaction [8] in water.

### 2. Experimental

2.1. General Procedures. All nonaqueous reactions were conducted under an atmosphere of nitrogen with magnetic stirring. Tetrahydrofuran (THF), dichloromethane (CH₂Cl₂), acetonitrile (MeCN), and diethyl ether (Et₂O) were dried by distillation and stored over activated molecular sieves. Dehydrated methanol (MeOH) was purchased from Kanto Chemical (Tokyo, Japan). Dimethyl sulfoxide (DMSO) was purchased from Wako Pure Chemical Industries (Osaka, Japan). All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ plates produced by Merck. Column chromatography was performed with acidic Silica gel 60 (spherical, 40–50 μm) or neutral Silica gel 60N (spherical, 40–50 μm) produced by Kanto Chemical.

Melting point was measured by an AS one ATM-01 apparatus. Infrared (IR) spectra were recorded on a JASCO FT-IR 4100 spectrometer and are reported in wavenumbers (cm⁻¹).
2. 1-Methoxy-4-Propylbenzene (3). To a suspension of 10% Pd/C (0.101 g) in MeOH (30 mL) under atmosphere of hydrogen was added 1-methoxy-4-(1-propenyl)benzene 2 (1.00 g, 6.75 mmol). After stirring for 3 h at room temperature, the reaction mixture was filtered through a pad of Celite with MeOH. Concentration in vacuo afforded 3 (0.957 g, 6.37 mmol, 94%) as a colorless oil; Rf 0.48 (hexane/EtOAc = 20:1); IR (neat) 3276.18, found 275.95; EI-HRMS (m/z) [M]+ calcd for C27H22O [M]+ 227.0072, found 227.0072.

2.2. 2-Bromo-1-Methoxy-4-Propylbenzene (4). To a solution of N-bromosuccinimide (0.498 g, 2.80 mmol, 1.2 eq) in MeCN (8.75 mL) was added 1-methoxy-4-propylbenzene 3 (0.351 g, 2.34 mmol, 1.0 eq). After stirring for 3 h at room temperature, the reaction mixture was concentrated in vacuo, and washed with CCl4. Concentration in vacuo afforded 4 (0.521 g, 2.27 mmol, 97%) as a colorless oil; Rf 0.61 (hexane/EtOAc = 20:1); IR (neat) 3276.18, found 275.95; EI-HRMS (m/z) [M]+ calcd for C26H19BrO [M]+ 292.01, found 292.01.

2.3. 2-Bromo-1-Methoxy-4-Propylbenzene (4). To a solution of N-bromosuccinimide (0.498 g, 2.80 mmol, 1.2 eq) in MeCN (8.75 mL) was added 1-methoxy-4-propylbenzene 3 (0.351 g, 2.34 mmol, 1.0 eq). After stirring for 3 h at room temperature, the reaction mixture was concentrated in vacuo, and washed with CCl4. Concentration in vacuo afforded 4 (0.521 g, 2.27 mmol, 97%) as a colorless oil; Rf 0.61 (hexane/EtOAc = 20:1); IR (neat) 3276.18, found 275.95; EI-HRMS (m/z) [M]+ calcd for C26H19BrO [M]+ 292.01, found 292.01.

2.4. 1-Methoxy-4-Propyl-2-(4,4,5,5-Tetramethyl-[1,3,2]Dioxaborolan-2-yl)Benzene (5). To a mixture of [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (47.7 mg, 0.0655 mmol, 5 mol%), bis(pinacolato)diboron (399 mg, 1.57 mmol, 1.2 eq), and potassium acetate (386 mg, 3.93 mmol, 3.0 eq) was added 2-bromo-1-methoxy-4-propylbenzene 4 (300 mg, 1.31 mmol, 1.0 eq) in DMSO (4.5 mL). After stirring for 24 h at 80°C, the reaction mixture was diluted with toluene and quenched with H2O. The aqueous layer was then extracted with toluene. The combined organic layers were washed with H2O, dried over Na2SO4, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc = 20:1) afforded 5 (110.3 mg, 0.399 mmol, 31%), 6 (17.0 mg, 0.0616 mmol, 5%), and 4 (69.3 mg, 0.303 mmol, 23%).

2.5. 2,2′-Dimethoxy-5,5′-Dipropyl-Biphenyl (6). To a mixture of 2-bromo-1-methoxy-4-propylbenzene 4 (413.3 mg, 0.180 mmol, 1.0 eq), 1-methoxy-4-propyl-2-(4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzene 5 (49.6 mg, 0.180 mmol, 1.0 eq), and tetrakis(triphenylphosphine) palladium(0) (10.4 mg, 0.0300 mmol, 5 mol%) was added potassium carbonate (74.6 mg, 0.54 mmol, 3.0 eq) in THF (2.0 mL). After stirring for 8 h at reflux, the reaction mixture was concentrated in vacuo and extracted with CH2Cl2. The combined organic layers were washed with H2O, dried over Na2SO4, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc = 20:1) afforded 6 (11.3 mg, 0.0258 mmol, 14%) as a yellow oil; Rf 0.38 (hexane/EtOAc = 10:1); IR (neat) 3276.18, found 227.95; EI-HRMS (m/z) calcd for C36H33BrO [M]+ 551.18, found 551.0.

*Figure 1: Structures of magnolignan (1), magnolol, and honokiol.*
7.5 Hz, CH₂), 1.57–1.70 (4H, m, CH₂), 0.95 (6H, t, J = 7.1 Hz, CH₃); 13C NMR (75 MHz, CDCl₃) δ 155.2, 134.5, 131.7, 128.3, 127.8, 111.1, 56.0, 37.3, 24.8, 14.0; GC-MS (m/z) calcd for C₂₈H₃₂O₂ [M⁺] 298.19, found 298.20; EI-HRMS (m/z) calcd for C₂₈H₃₂O₂ [M⁺] 298.1933, found 298.1930.

2.6. 2-Methoxy-5-Propargylphosphonic Acid (7). To a solution of 2-bromo-1-methoxy-4-propylbenzene 4 (200 mg, 0.873 mmol, 1.0 eq) in THF (3.6 mL) was added 1.6 M n-BuLi in hexane (0.709 mL, 1.135 mmol, 1.3 eq) at −78 °C. After stirring for 5 min, triisopropyl borate (0.586 mL, 2.619 mmol, 3.0 eq) was added at −78 °C and the mixture was allowed to warm up to room temperature. After stirring for 13 h at room temperature, the reaction mixture was acidified with 10% HCl aq. and extracted with EtOAc. The combined organic layers were washed with H₂O, dried over Na₂SO₄, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc = 13:1) afforded 7 (114.6 mg, 0.591 mmol, 68%) and 3 (23.6 mg, 0.157 mmol, 18%). 7 was obtained as a colorless powder; Rf 0.33 (hexane/EtOAc = 3:1); mp 71 °C; IR (KBr) νmax 3801, 3358, 2926, 2355, 1607, 1415, 1338, 1229, 1155, 1097, 1043, 788, 679, 555 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 7.64 (1H, d, J = 2.3 Hz, ArH), 7.23 (1H, d, J = 2.3 Hz, ArH), 6.84 (1H, d, J = 8.4 Hz, ArH), 3.89 (3H, s, OMe), 2.55 (2H, t, J = 7.1 Hz, CH₂). 13C NMR (75 MHz, CDCl₃) δ 162.8, 136.8, 135.3, 132.8, 131.7, 128.3, 127.8, 111.1, 56.0, 37.3, 24.8, 14.0; GC-MS (m/z) calcd for C₁₈H₁₅BO₃ [M⁺] 298.1914, found 298.1905.

2.7. 2,2′-Dimethoxy-5,5′-Dipropyl-Biphenyl (6). To a mixture of 2-bromo-1-methoxy-4-propylbenzene 4 (50.5 mg, 0.220 mmol, 1.0 eq) and 2-methoxy-5-propargylphosphonic acid 7 (55.4 mg, 0.287 mmol, 1.3 eq) were added palladium(II) acetate (0.01 mg, 0.437 μmol, 0.2 mol%), potassium carbonate (75.0 mg, 0.546 mmol, 2.5 eq), and tetrabutylammonium bromide (70.0 mg, 0.218 mmol, 1.0 eq) in H₂O (0.23 mL). The reaction mixture was degassed by freeze/pump/thaw techniques. After stirring for 2 h at 70 °C, the reaction mixture was cooled to room temperature, diluted with H₂O, and then extracted with EtOAc. The combined organic layers were washed with H₂O, dried over Na₂SO₄, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc = 80:1) afforded 6 (63.7 mg, 0.213 mmol, 98%).

2.8. 2,2′-Dihydroxy-5,5′-Dipropyl-Biphenyl (1). To a solution of 2,2′-dimethoxy-5,5′-dipropyl-biphenyl 6 (24.2 mg, 0.081 mmol, 1.0 eq) in CH₂Cl₂ (1.4 mL) was added 1 M boron tribromide in CH₂Cl₂ (0.406 mL, 0.406 mmol, 5.0 eq) at −78 °C, then allowed to warm up to room temperature. After stirring for 1.5 h, the reaction mixture was quenched carefully with 10% HCl aq. at 0 °C and extracted with Et₂O. The combined organic layers were washed with H₂O, dried over Na₂SO₄, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc = 20:1) afforded 1 (18.3 mg, 0.068 mmol, 83%) as a colorless powder; Rf 0.43 (hexane/EtOAc = 3:1); mp 144 °C; IR (KBr) νmax 3206, 2963, 2923, 2855, 1494, 1415, 1226, 1113, 887, 818, 797, 598, 534, 438 cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ 7.13 (2H, dd, J = 8.0, 2.3 Hz, ArH), 7.06 (2H, d, J = 2.3 Hz, ArH), 6.95 (2H, d, J = 8.0 Hz, ArH), 2.57 (4H, t, J = 7.5 Hz, CH₂), 1.60–1.67 (4H, m, CH₂), 0.95 (6H, t, J = 7.5 Hz, CH₃); 13C NMR (125 MHz, CDCl₃) δ 151.0, 136.0, 131.1, 130.0, 123.4, 116.5, 37.3, 24.9, 14.0; EI-HRMS (m/z) calcd for C₁₈H₂₂O₂ [M⁺] 270.1620, found 270.1613.

3. Results and Discussion

Starting with commercially available trans-anethole (2), the synthesis of 1 involved hydrogenation, bromination, boronation, Suzuki-Miyaura reaction, and demethylation, as illustrated in Scheme 1. Initially, direct bromination of 2 using N-bromosuccinimide (NBS) was intended as the first step in the synthesis. However, this reaction did not proceed. Therefore, alkene 2 was reduced by H₂ with Pd/C to give alkane 3 in 94% yield [9]. Obtained 3 was then converted to bromide 4 in good yield (70–80%, data not shown) using NBS and HBF₄·Et₂O in MeCN at −20 °C to room temperature [10]. However, the product was a mixture of monobromide 4 and the dibromide compound. It was thought that acidic condition prompted the reactivity of the bromination. Therefore, the reaction was attempted with 1.2 equivalents of NBS without additives in MeCN at room temperature. The desired compound 4 was obtained as a single product in 97% yield [11].

Next, the transformation of bromide 4 into arylboronate ester 5 was pursued. Unfortunately, in a one pot reaction using (Bpin)₂ in the presence of 5 mol% PdCl₂(dppf) and AcOK in DMSO at 80 °C, compound 5 was obtained in only 31% yield along with biaryl compound 6 in 5% yield and recovered starting material 4 in 23% yield [12]. Although the yield for compound 6 could not be improved in this reaction, biaryl product 6 was synthesized in 14% yield through a Suzuki-Miyaura cross-coupling reaction between 4 and 5 in the presence of 5 mol% Pd(PPh₃)₄ and K₂CO₃ in THF under reflux condition [13].

As an alternative strategy, arylboronic acid 7 was prepared from bromide 4 as a precursor for the Suzuki-Miyaura reaction (Scheme 1). Bromide 4 was thus converted into 7 with n-BuLi and triisopropyl borate in 68% yield, with alkene 3 as a by-product in 18% yield [14]. The Suzuki-Miyaura cross-coupling reaction between 4 and 7 then afforded biaryl product 6 in 98% yield using 0.2 mol% Pd(OAc)₂ in H₂O at 70 °C in the presence of one equivalent of tetrabutylammonium bromide (TBAB) as a phase transfer catalyst [15]. This reaction was achieved as an eco-friendly system with a high yield. Finally, removal of the methyl group from 6 using BBr₃ in CH₂Cl₂ at −78 °C to room temperature gave the desired magnolignan 1 in 83% yield [16]. Synthetic 1 was fully assigned by spectroscopic analysis, including 1H NMR, 13C NMR, IR, and EI-HRMS [3].

In conclusion, the total synthesis of magnolignan 1, a new skin lightening component for use in cosmetics, was achieved in five steps with overall 50% yield. An aqueous Suzuki-Miyaura reaction was the key step in the synthesis.
The palladium-catalyzed Suzuki-Miyaura reaction in H₂O was achieved with excellent yield, and can be considered an eco-friendly reaction. Through variation of the Suzuki-Miyaura coupling precursors, this synthetic strategy is well suited for the preparation of a wide range of magnolignan derivatives for use in further SAR studies.

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References


