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SYNTHESIS OF GRAPHISLACTONE H

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Abstract – Short step synthesis of graphislactone H was achieved through a palladium-mediated aryl-aryl coupling reaction.

Highly oxygenated 6*H*-dibenzo[*b,d*]pyran-6-one[1] is an important ring system because some compounds possessing this skeleton often exhibit interesting biological activities.[2] Among such compounds, graphislactone H (**1**), which was isolated from *Cephalosporium acremonium* IFB-E007 in 2005, is known to exhibit anticancer activity against SW1116 cells.[3]

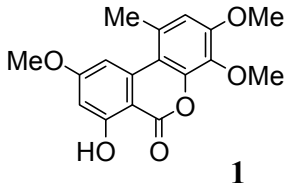

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Figure 1. Structure of graphislactone H

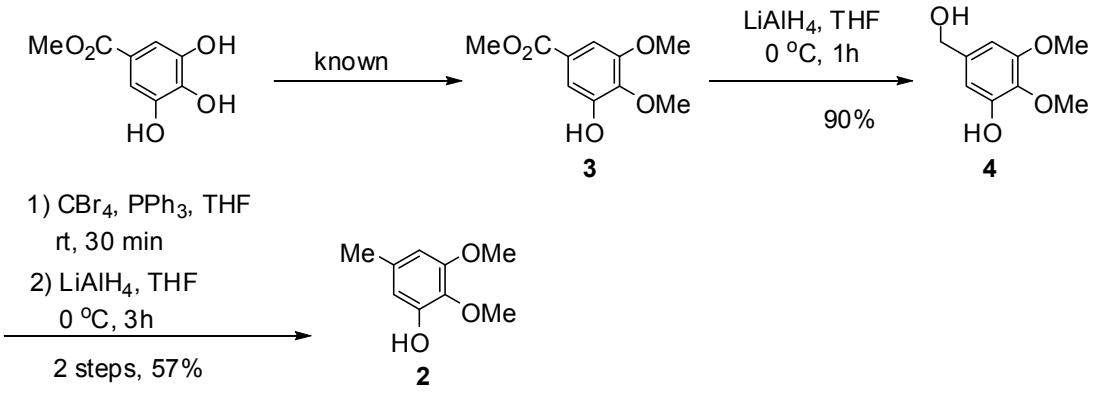
In 2009, Podlech *et al.* reported the synthesis of graphislactone H *via* the Suzuki-Miyaura coupling reaction and concomitant lactonization.[4] Although their synthetic scheme is quite reasonable, the modest yield of the lactonization step should be improved. In this article, we describe an alternative synthesis of graphislactone H, through an intramolecular biaryl coupling reaction of a phenyl benzoate derivative using a palladium reagent.[5]

Initially, we needed to prepare phenol (**2**) as an essential part of phenyl benzoate. According to the known method,[6] methyl gallate was transformed into the phenol (**3**), which was reduced with lithium aluminum hydride to the corresponding benzyl alcohol (**4**)[7] (Scheme 1). The benzylic hydroxyl group was reduced to a methyl group by way of benzyl bromide, producing the desired phenol (**2**).[8]

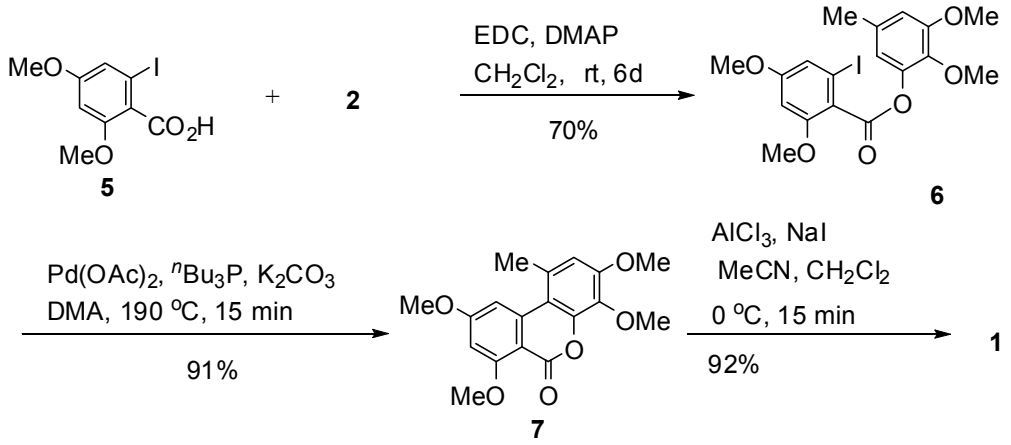
This paper is dedicated to Professor Dr. Albert Eschenmoser on occasion of his 85th birthday.

On the other hand, the necessary benzoic acid (**5**) has already been prepared in our laboratory.[5c] Esterification between **2** and **5** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) was successful to form the key precursor (**6**) for the biaryl coupling reaction (Scheme 2). The coupling reaction using a $Pd(OAc)_2$-$^nBu_3P$-K_2CO_3 combination proceeded smoothly to afford the tricyclic **7**. For the selective demethylation, Node's protocol[9] was employed to complete the synthesis of graphislactone H (**1**). The spectral data for the synthetic compound are in accordance with the data provided in the literature.[3]

In summary, we synthesized graphislactone H *via* a Pd-mediated intramolecular biaryl coupling reaction of a phenyl benzoate derivative. Our synthetic scheme would be widely applicable for other 6*H*-dibenzo[*b*,*d*]pyran-6-one derivatives.



Scheme 1. Preparation of phenol (**2**)



Scheme 2. Synthesis of graphislactone H

EXPERIMENTAL

General: Melting points were measured using a Yanagimoto micro melting point hot-plate apparatus and are uncorrected. The IR spectra were recorded using a JASCO FTIR-350 spectrophotometer. The

NMR spectra were obtained using a Varian MERCURY-300 instrument with the chemical shifts being reported as δ ppm and the couplings expressed in Hertz. Elemental analysis as performed with a Yanaco MT-5 analyzer. Silica gel column chromatography was carried out using Daisogel 1002W or Merck 9385 Kieselgel 60. All reactions were carried out under an argon atmosphere.

Methyl 3-hydroxy-4,5-dimethoxybenzoate (**3**) was prepared from methyl gallate by the reported procedure.[6]

3-Hydroxy-4,5-dimethoxybenzyl alcohol (**4**). To a mixture of $LiAlH_4$ (0.72 g, 18.9 mmol) and THF (5 mL), a solution of **3** (2.00 g, 9.43 mmol) in THF (10 mL) was added dropwise at 0 °C, and the mixture was then stirred for 1 h at the same temperature. After a 10% NaOH aqueous solution was added to the mixture, 10% HCl aqueous solution was added to acidify the mixture. Extraction with Et_2O, drying over $MgSO_4$, and evaporation gave a residue that was recrystallized from AcOEt-Et_2O to afford **4** (1.56 g, 90%) as colorless needles, mp 108-109 °C [lit.,[7] mp 94-96 °C]. IR (KBr) cm^{-1}: 3400, 3240, 1600, 1510, 1470, 1430, 1360, 1240, 1200, 1170, 1140, 1110.^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.87 (3H, s, Ar-OMe), 3.89 (3H, s, Ar-OMe), 4.59 (2H, d, J = 5.7 Hz, Ar-OCH_2OH), 5.79 (1H, bs, OH), 6.53 (1H, d, J = 1.8 Hz, H-2 or H-6), 6.60 (1H, d, J = 1.8 Hz, H-2 or H-6).

2,3-Dimethoxy-5-methylphenol (**2**). To a solution of **4** (200 mg, 1.09 mmol) in THF (5 mL), CBr_4 (544 mg, 1.64 mmol) and PPh_3 (429 mg, 1.64 mmol) were added, and the mixture was stirred for 30 min at rt. After MeOH and H_2O were added, the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give an yellow residue. A solution of the residue in THF (3mL) was added dropwise to a suspension of $LiAlH_4$ (167 mg, 4.39 mmol) and THF (3 mL) at 0 °C. After stirring for 3 h at the same temperature, 10% NaOH aqueous solution was added to the mixture. A 10% HCl aqueous solution was added to acidify the mixture which was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a yellow residue that was subjected to column chromatography with AcOEt-hexane (1:3). Colorless needles of **2** (104 mg, 57%) were obtained, mp 55-56.5 °C (AcOEt-hexane) [lit.,[8] mp 49-51 °C]. IR (KBr) cm^{-1}: 3380, 1600, 1510, 1460, 1355, 1240, 1240, 1200, 1170, 1100, 990. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.27 (3H, s, Me), 3.84 (3H, s, OMe), 3.86 (3H, s, OMe), 5.69 (1H, bs, OH), 6.29 (1H, d, J = 1.5 Hz, H-2 or H-6), 6.42 (1H, d, J = 1.5 Hz, H-2 or H-6).

2,3-Dimethoxy-5-methylphenyl 2-iodo-4,6-dimethoxybenzoate (**6**). Under an argon atmosphere, a solution of **5** (240 mg, 0.78 mmol), **2** (70.0 mg, 0.42 mmol), EDC (319 mg, 1.66 mmol), and DMAP (186 mg, 1.52 mmol) in CH_2Cl_2 (MeOH-free, 1 mL) was stirred for 6 d at rt. The reaction mixture was poured into water and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue that was subjected to silica gel column chromatography with

AcOEt-hexane (1:3). After recrystallization from CH_2Cl_2-Et_2O, colorless needles of **6** (135 mg, 70%) were obtained, mp 119—120 °C. IR (KBr) cm^{-1}: 1750, 1600, 1560, 1510, 1460, 1250, 1225, 1155, 1095, 1040, 1025. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.34 (3H, s, Me), 3.82 (3H, s, 4-OMe), 3.87 (each 3H, s, 2',3',6-OMe), 6.49 (1H, d, *J* = 2.1 Hz, H-5), 6.65 (1H, d, *J* = 2.0 Hz, H-6'), 6.73 (1H, dd, *J* = 2.0 Hz, 0.6 Hz, H-4'), 6.97 (1H, d, *J* = 2.1 Hz, H-3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 21.4, 55.7, 56.1, 56.1, 61.1, 92.9, 99.0, 111.2, 115.4 (2×C), 122.4, 133.6, 139.1, 143.7, 153.4, 158.3, 161.8, 165.7. *Anal.* Calcd for $C_{18}H_{19}O_6I$: C, 47.18; H, 4.18. Found: C, 47.29; H, 4.20.

3,4,7,9-Tetramethoxy-1-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one (7). A mixture of **6** (115 mg, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.03 mmol), K_2CO_3 (34.7 mg, 0.25 mmol), ^{n}Bu_3P (12.5 μL, 0.05 mmol), and DMA (3 mL) was heated at 190 °C. After 15 min, the mixture was cooled to rt, diluted with AcOEt, and filtered to remove the solid materials. The filtrate was poured into H_2O and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a brown residue. Purification by silica gel column chromatography with AcOEt-hexane (1:1) yielded **7** (75.0 mg, 91%). Colorless needles, mp 210—211 °C (CH_2Cl_2). IR (KBr) cm^{-1}: 1710, 1600, 1580, 1480, 1460, 1330, 1230, 1220, 1130. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.80 (3H, s, Me), 3.94 (3H, s, 9-OMe), 3.95 (3H, s, 3-OMe), 3.96 (3H, s, 4-OMe), 4.00 (3H, s, 7-OMe), 6.55 (1H, d, *J* = 2.4 Hz, H-8), 6.69 (1H, s, H-2), 7.25 (1H, d, *J* = 2.4 Hz, H-10). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 25.6, 55.5, 56.1, 56.4, 61.4, 97.2, 102.6, 103.5, 112.0, 112.1, 130.8, 134.5, 140.6, 146.8, 152.5, 157.2, 163.9, 164.6. *Anal.* Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.27; H, 5.57.

Graphislactone H (**7-Hydroxy-3,4,9-trimethoxy-1-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one**) (**1**). To a solution of **7** (80.0 mg, 0.24 mmol) in MeCN (2 mL) and CH_2Cl_2 (4 mL), $AlCl_3$ (162 mg, 1.21 mmol) and NaI (127 mg, 0.85 mmol) were added at 0 °C, and the mixture was stirred for 15 min at the same temperature. After 5% aqueous $Na_2S_2O_3$ solution was added, the mixture was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and evaporated. The resultant solid was recrystallized from CH_2Cl_2-Et_2O to yield **1** (70.4 mg, 92%) as colorless needles, mp 196—197 °C [lit.,[3] mp 165—166 °C, lit.,[4] mp 179-181 °C]. IR (KBr) cm^{-1}: 2964, 2940, 2845, 1664, 1630, 1602, 1580, 1460, 1440, 1400, 1350, 1250, 1240, 1215, 1140, 830, 800, 780. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.79 (3H, s, Me), 3.91 (3H, s, 9-OMe), 3.95 (3H, s, 3-OMe), 3.96 (3H, s, 4-OMe), 6.55 (1H, d, *J* = 2.0 Hz, H-8), 6.73 (1H, s, H-2), 7.24 (1H, d, *J* = 2.0 Hz, H-10) 11.95 (1H, bs, OH, exchangeable with D_2O). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 25.8 (Me), 55.7 (9-OMe), 56.1 (3-OMe), 61.5 (4-OMe), 99.1 (C-8), 99.2 (C-6a), 104.8 (C-10), 111.7 (C-10b), 112.9 (C-2), 131.7 (C-1), 135.1 (C-4), 137.9 (C-10a), 146.0 (C-4a), 152.6 (C-3), 164.9 (C-6), 165.1 (C-7), 166.3 (C-9). *Anal.* Calcd for $C_{17}H_{16}O_6 \cdot 1/4H_2O$: C, 63.65; H, 5.18. Found: C, 63.42; H, 5.07.

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