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SYNTHESIS OF NIGRICANIN VIA INTRAMOLECULAR BIARYL COUPLING REACTION OF FUNCTIONALIZED PHENYL BENZOATE

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Abstract – A tetracyclic natural product, nigricanin (**1**), was synthesized through an intramolecular biaryl coupling reaction of the phenyl benzoate derivative which was derived from the corresponding phenol and benzoic acid.

INTRODUCTION

Ellagic acid and its family are well known to exhibit a wide range of biological activities, such as antioxidant[1] and anti-cancer properties.[2] Because of their polyphenolic structures, ellagic acid and its derivatives act as free radical scavengers and thus are utilized in anti-aging supplements.[3] Nigricanin (**1**) is one of the ellagic acid congeners, which was isolated from *Russula nigricans*, and its chemical structure was determined in 2004 (Figure 1).[4] Although there are several methods for the synthesis of ellagic acid,[5] the synthesis of **1** has never been reported in spite of its unique structure and suspected biological interest.

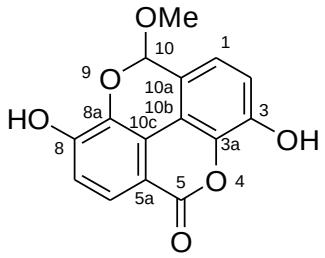


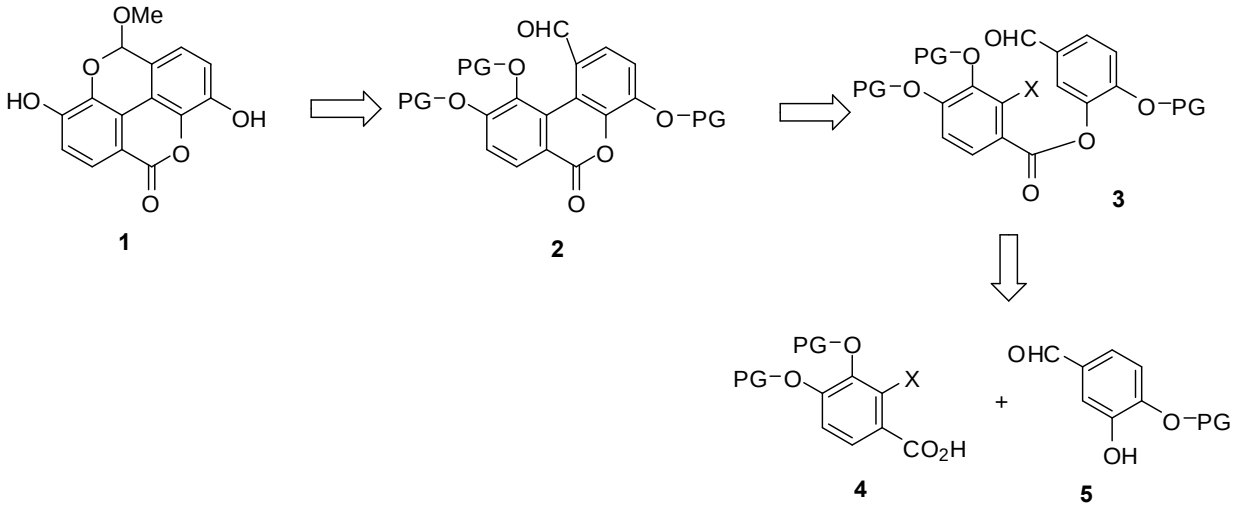
Figure 1. Structure of Nigricanin (**1**)

In this article, we report the first synthesis of **1** *via* the intramolecular biaryl coupling reaction of a phenyl benzoate derivative.[6]

RESULTS AND DISCUSSION

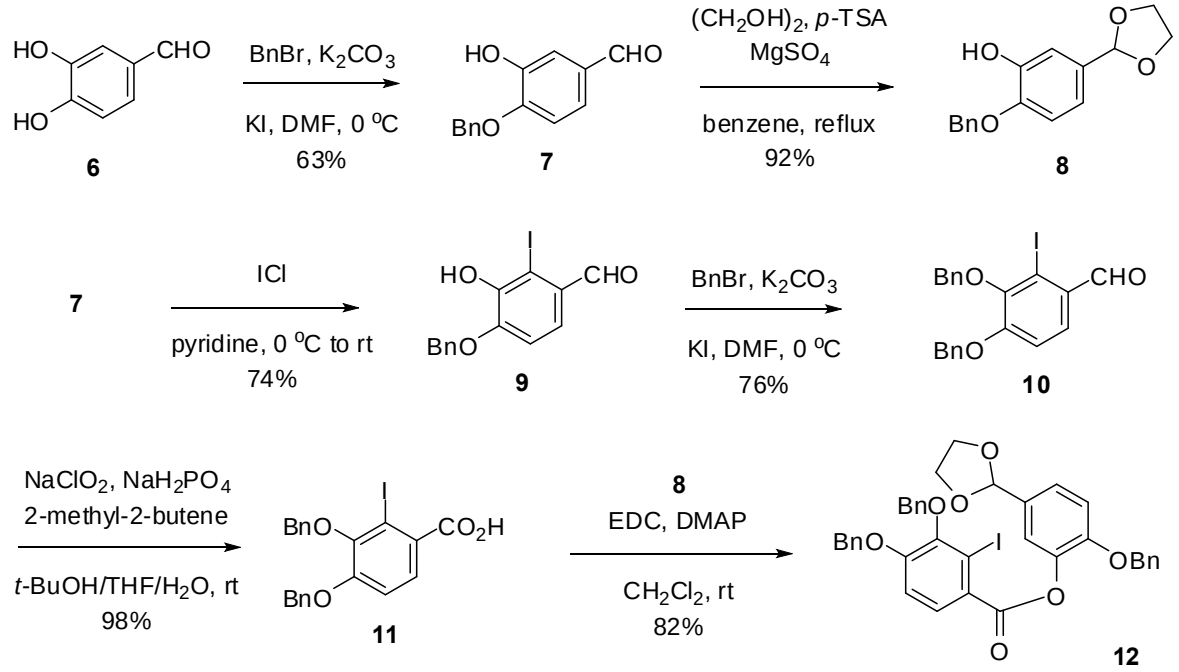
Based on the retrosynthesis depicted in Scheme 1, we planned to prepare the lactone compound **2** as the precursor of the target molecule, nigricanin **1**. The lactone **2** should be realized by the intramolecular

biaryl coupling reaction of the functionalized phenyl benzoate **3**, which can be simply prepared from the corresponding benzoic acid **4** and phenol **5**.



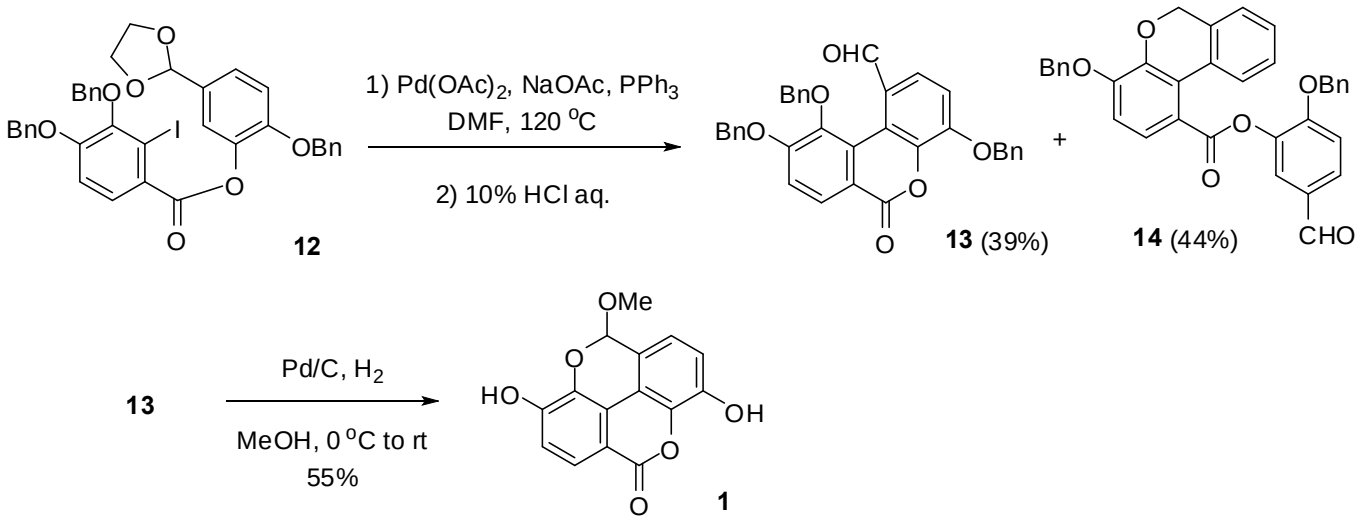
Scheme 1. Retrosynthesis of Nigricanin (**1**)

Synthesis of **1** commenced with the preparation of the phenol part by a two-step conversion from 3,4-dihydroxybenzaldehyde (**6**), involving the selective benzylation of **6** into **7**, followed by the protection of the formyl group with ethylene glycol to afford **8** (Scheme 2). The monobenzyl compound **7** was also regioselectively iodinated with ICl into **9**, which was benzylated again, to generate **10**. The aldehyde **10** was oxidized with $NaClO_2$ for the generation of the desired benzoic acid **11**, and then the coupling precursor **12** was prepared by a simple esterification between **8** and **11**.



Scheme 2. Preparation of Ester **12**

To construct the lactone ring, we examined the palladium-mediated intramolecular coupling reaction with **12** ($Pd(OAc)_2$, NaOAc, PPh_3, DMF, 120 °C) (Scheme 3). During the work-up stage, the ethylenedioxy group was deprotected, thus the tricyclic formyl compound **13** was produced in 39% yield. However, a byproduct **14** (44%) was also generated in this step. The undesired **14** was a chemo-isomer of **13**, namely, the protecting benzyloxy group at the position *ortho* to the iodo function reacted under the employed reaction conditions.[7] In spite of the moderate yield of **13**, the catalytic hydrogenation of **13** in methanol successfully produced the target molecule, nigricanin **1**.

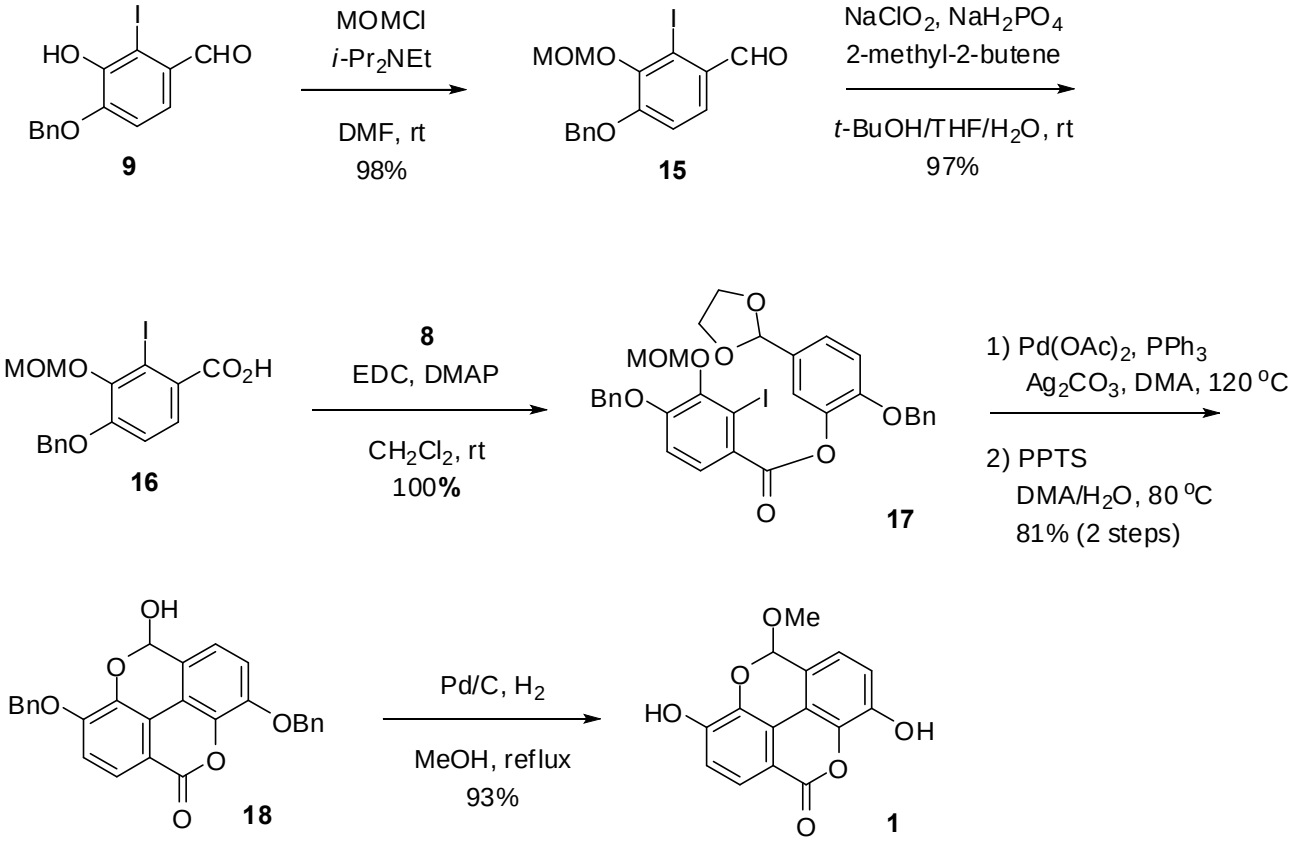


Scheme 3. Pd-Mediated Biaryl Coupling and Conversion into Nigricanin (**1**)

In order to avoid the participation of the protecting group during the key coupling reaction, we postulated that the MOM protection would be suitable at the 3-position of the benzoyl moiety (Scheme 4). Thus, **9** was protected with the MOM group to form **15** followed by the oxidation of the formyl group, then the esterification between **16** and **8** furnished the coupling precursor **17**. The coupling reaction of **17** proceeded under conditions as illustrated in Scheme 4 ($Pd(OAc)_2$, Ag_2CO_3, PPh_3, DMA, 120 °C), then the acidic work-up removed the two acetal functions to afford a tetracyclic product **18**. The final deprotection of the benzyl group by conventional hydrogenolysis afforded nigricanin (**1**). The comparison of the NMR data of both the synthetic and reported[4] ones is listed in Table 1. Consequently, these NMR data are identical, therefore, the synthesis of nigricanin was completed.

CONCLUSION

The synthesis of nigricanin (**1**) was achieved through the palladium-mediated biaryl coupling reaction of the phenyl benzoates as the key step. Progress toward the synthesis of these types of natural products will be reported in due course.



Scheme 4. Improved Synthesis of Nigricanin (1)

Table 1. Comparison of ^{1}H- and ^{13}C-NMR data

	^{1}H		^{13}C	
position	synthetic	reported [ref.4]	synthetic	reported [ref.4]
1	7.22 (d, *J* = 8.4)	7.21 (d, *J* = 9.5)	123.0	123.0
2	7.14 (d, *J* = 8.4)	7.13 (d, *J* = 9.5)	118.3	118.4
3			145.6	145.6
3a			120.4	120.5
5			160.0	160.1
5a			112.0	112.2
6	7.80 (d, *J* = 8.8)	7.79 (d, *J* = 10)	124.8	124.8
7	7.20 (d, *J* = 8.8)	7.18 (d, *J* = 10)	119.0	119.0
8			151.8	151.8
8a			135.9	136.1
10	6.35 (s)	---[a)]	99.7	99.1
10a			138.2	138.3
10b			112.9	113.1
10c			121.8	121.9
MeO	3.58 (s)	3.57 (s)	56.0	56.0

a) No data was given.

EXPERIMENTAL

General Information

Melting points were measured using a Yanagimoto micro-melting point hot-plate and are uncorrected. The IR spectra were recoded using a Jasco FTIR-350 or FTIR-4100 spectrophotometer. The NMR spectra were obtained using a Varian VXR-500 (500 MHz), or JEOL α-400 (400 MHz) instrument. The chemical shifts are given in δ parts per million with TMS as an internal standard. The elemental analyses were performed using a Yanaco MT-5 or Elementar vario MICRO cube analyzer. The FABMS was obtained using a VG-70SE or JEOL JMS-AX505HAD instrument with *m*-nitrobenzyl alcohol as the matrix. The EIMS was obtained using a JEOL JMS-700 or JMS-GCmate II instrument. Silica gel column chromatography was carried out using wakogel® C-200 (Wako) or 9385 Kieselgel 60 (Merck). TLC analysis was performed on Kieselgel 60 F_{254} (Merck) plates. Solvents were dried with a standard procedure.

4-Benzyloxy-3-hydroxybenzaldehyde (7)[8]

To a mixture of **6** (8.21 g, 59.4 mmol), K_2CO_3 (9.04 g, 65.4 mmol), KI (0.496 g, 2.99 mmol), and DMF (10 mL), benzyl bromide (7.60 mL, 64.0 mmol) was dropwise added at 0 °C. The mixture was stirred for 22 h at the same temperature, then acidified with 10% HCl aq. After extraction with ether, the organic layer was washed with brine and dried over $MgSO_4$. The organic solvent was removed in vacuo to give a residue which was purified by silica gel column chromatography (15/1 to 4/1: AcOEt/hexane). The obtained solid was recrystallized from AcOEt/hexane to provide colorless prisms of **7** (8.48 g, 63%): mp 120.1-121.0 ºC (AcOEt−hexane) [lit.,[8] mp 118-120 ºC]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H, ArCHO), 7.46 (d, *J* = 2.0 Hz, 1H, ArH), 7.44-7.37 (m, 6H, ArH), 7.04 (d, *J* = 8.8 Hz, 1H, ArH), 5.80 (s, 1H, ArOH), 5.21 (s, 2H, $ArCH_2$-).

5-(1,3-Dioxolan-2-yl)-2-benzyloxyphenol (8)[9]

Using a Dean-Stark apparatus, a mixture of **7** (1.51 g, 6.60 mmol), ethylene glycol (1.82 mL, 32.8 mmol), *p*-TsOH (monohydrate, 119 mg, 0.69 mmol), $MgSO_4$ (4.03 g, 33.5 mmol), and dry benzene (30 mL) was heated under reflux for 18 h. The mixture was poured into 10% $NaHCO_3$ aq. and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue, which was recrystallized from CH_2Cl_2-Et_2O. Colorless needles of **8** (1.66 g, 92%) were obtained: mp 84.5-86.5 °C (CH_2Cl_2-Et_2O). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43-7.34 (m, 5H, ArH), 7.08 (d, *J* = 2.0 Hz, 1H, ArH), 6.96 (dd, *J* = 8.2, 2.0 Hz, 1H, ArH), 6.91 (d, *J* = 8.2 Hz, 1H, ArH), 5.73 (s, 1H, ArOH), 5.68 (s, 1H, ArCH-), 5.22 (s, 2H, $ArCH_2$-), 4.16-3.97 (m, 4H, -OCH_2CH_2O-).

4-Benzyloxy-3-hydroxy-2-iodobenzaldehyde (9)

To a solution of **7** (8.45 g, 37.0 mmol) in pyridine (80 mL), ICl (2.3 mL, 44.0 mmol) was added at 0 °C, then the mixture was stirred for 4 days at the same temperature. After it was warmed to room temperature, the mixture was stirred for 4 h at rt, then 10% HCl aq. was added to acidify the mixture, which was then extracted with AcOEt. The organic layer was washed with 10% $Na_2S_2O_3$ aq. and brine, then dried over $MgSO_4$ and evaporated to give a crude residue. After silica gel column chromatography (20/1/2 to 5/1/4: AcOEt/hexane/$CHCl_3$), the obtained solid material was recrystallized from AcOEt to provide light yellow needles of **9** (9.66 g, 74%): mp 126.2-127.2 °C (AcOEt). IR (KBr) υ_{max} 3062-2789, 2640, 2568, 1685, 1577, 1476, 1421, 1382, 1308, 1274, 1162, 1082, 1012, 997, 977, 921, 900, 828, 778, 743, 698, 676 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H, ArCHO), 7.53 (d, *J* = 8.2 Hz, 1H, ArH), 7.46-7.37 (m, 5H, ArH), 6.98 (d, *J* = 8.2 Hz, 1H, ArH), 6.36 (s, 1H, ArOH), 5.22 (s, 2H, $ArCH_2$-). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 195.0, 149.9, 146.0, 134.9, 129.0, 129.0, 128.9, 128.0, 123.7, 111.4, 88.5, 71.7. *Anal.* Calcd for $C_{14}H_{11}IO_3$: C, 47.48; H, 3.13. Found: C, 47.31; H, 3.33.

3,4-Benzyloxy-2-iodobenzaldehyde (10)

A solution of **9** (4.01 g, 11.3 mmol), K_2CO_3 (1.76 g, 12.7 mmol), DMF (45mL), and a portion of KI was stirred for 30 min at 0 °C. Benzyl bromide (1.34 mL, 11.3 mmol) was added to the solution, and stirred for 6 h at 0 °C. The mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue which was recrystallized from AcOEt. Flesh-colored crystals of **10** (3.81 g, 76%) were provided. For an analytical sample, further recrystallization was carried out from Et_2O-hexane: mp 129.8-130.8 °C (Et_2O-hexane). IR (KBr) υ_{max} 2934, 2893, 2845, 1739, 1620, 1577, 1517, 1477, 1442, 1389, 1304, 1272, 1222, 1211, 1160, 1125, 1084, 1017, 917, 825, 819, 770, 761, 737 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H, ArCHO), 7.72 (d, *J* = 8.6 Hz, 1H, ArH), 7.50-7.28 (m, 10H, ArH), 7.07 (d, *J* = 8.6 Hz, 1H, ArH), 5.23 (s, 2H, $ArCH_2$-), 5.05 (s, 2H, $ArCH_2$-). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 195.1, 157.0, 148.0, 136.6, 135.6, 129.4, 128.90, 128.88, 128.6, 128.5, 128.4, 127.7, 127.5, 113.4, 101.2, 74.7, 71.3. *Anal*. Calcd for $C_{21}H_{17}IO_3$: C, 56.77; H, 3.86. Found: C, 56.55 ; H, 4.09.

3,4-Dibenzyloxy-2-iodobenzoic acid (11)

To a solution of **10** (511 mg, 1.15 mmol) and 2-methyl-2-butene (5.0 mL, 42.3 mmol) in a mixed solvent of *t*-BuOH, THF, and H_2O (13:12:1, 65 mL), a solution of $NaH_2PO_4 \cdot 2H_2O$ (1.24 g, 7.92 mmol) and $NaClO_2$ (1.20 g, 10.5 mmol) in water (20 mL) was dropwise added and allowed to stand for 3 h. After evaporation of the organic solvent, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a yellow solid. Recrystallization from

AcOEt-hexane produced pure **11** (520 mg, 98%) as colorless prisms, mp 214.1-215.4 °C (hexane-AcOEt). IR (KBr) υ_{max} 3031, 2940, 2886, 1695, 1576, 1418, 1361, 1268, 1148, 1014, 978, 901, 773, 750, 734, 695, 671 cm^{-1}. ^{1}H-NMR (500 MHz, d_6-DMSO) δ 7.56-7.33 (m, 12H, ArH), 7.27 (d, *J* = 9.0 Hz, 1H, ArH), 5.26 (s, 2H, $ArCH_2Ph$), 4.93 (s, 2H, $ArCH_2Ph$). ^{13}C-NMR (125 MHz, d_6-DMSO) δ 167.6, 153.4, 147.7, 136.8, 136.2, 129.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.2, 113.4, 94.8, 73.5, 70.3. *Anal.* Calcd for $C_{21}H_{17}IO_4$: C, 54.80; H, 3.72. Found: C, 54.76; H, 3.68.

2-Benzyloxy-5-(1,3-dioxolan-2-yl)phenyl 3,4-dibenzyloxy-2-iodobenzoate (12)

Under an N_2 atmosphere, to a solution of **11** (1.40 g, 3.03 mmol) in CH_2Cl_2 (50 mL), DMAP (0.19 g, 1.54 mmol), EDC (0.87 g, 4.54 mmol), and **8** (0.83 g, 3.05 mmol) were successively added. The mixture was stirred for 3 h at room temperature, poured into ice water, neutralized with sat. $NaHCO_3$ aq., then extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated to give a residue which was recrystallized from Et_2O. Colorless needles of **12** (1.78 g, 82%) were then obtained: mp 135.2-136.3 °C; IR (KBr) υ_{max} 3056, 3033, 2880, 1733, 1579, 1510, 1455, 1390, 1372, 1272, 1124, 1012, 997, 807, 747, 699 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.8 Hz, 1H, ArH), 7.54-7.23 (m, 17H, ArH), 7.03 (d, *J* = 8.4 Hz, 1H, ArH), 6.96 (d, *J* = 8.8 Hz, 1H, ArH), 5.81 (s, 1H, ArCH-), 5.20 (s, 2H, $ArCH_2$-), 5.13 (s, 2H, $ArCH_2$-), 5.03 (s, 2H, $ArCH_2$-), 4.13-4.00 (m, 4H, $-OCH_2CH_2O-$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.9, 154.8, 151.1, 149.1, 140.3, 136.8, 136.6, 135.9, 131.3, 129.0, 128.9, 128.8, 128.5, 128.45, 128.43, 128.3, 127.9, 127.6, 127.4, 127.2, 125.2, 121.4, 113.7, 113.0, 103.1, 96.0, 74.5, 71.1, 70.8, 65.3. *Anal.* Calcd for $C_{37}H_{31}IO_7$: C, 62.19; H, 4.37. Found: C, 62.36; H, 4.52.

Intramolecular coupling reaction of 12

A mixture of **12** (50.8 mg, 0.0711 mmol), $Pd(OAc)_2$ (4.0 mg, 0.0178 mmol), NaOAc (11.7 mg, 0.143 mmol), PPh_3 (9.3 mg, 0.0355 mmol), and DMF (1.5 mL) was stirred for 1.5 h at 120 °C, then cooled to room temperature. To the mixture, 10% HCl aq. (1.5 mL) was added and stirred for 10 min. After the mixture was filtered, the filtrate was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated to give a residue which was subjected to silica gel column chromatography (benzene). Colorless prisms of **13** (14.9 mg, 39%) from the more polar fraction and an amorphous powder of **14** (16.9 mg, 44%) from the less polar fraction were obtained.

4,9,10-Ttribenzyloxy-1-formyl-*6H*-dibenzo[*b,d*]pyran-6-one (13): mp 171.8-172.8 °C (AcOEt). IR (KBr) υ_{max} 1728, 1676, 1591, 1562, 1497, 1445, 1379, 1281, 1242, 1200, 1132, 1105, 1003, 791, 733, 694, 411 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H, ArCHO), 8.11 (d, *J* = 8.8 Hz, 1H, ArH), 7.58 (d, *J* = 8.4 Hz, 1H, ArH), 7.45-6.76 (m, 17H, ArH), 5.22 (s, 2H, $ArOCH_2$), 5.17 (s, 2H, $ArOCH_2$), 4.63 (s,

2H, $ArOCH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 187.8, 160.1, 157.5, 149.8, 143.2, 141.1, 136.0, 135.5, 134.7, 129.6, 129.0, 128.9, 128.7, 128.5, 128.4, 128.2, 127.9, 127.7, 127.4, 127.2, 124.9, 117.6, 116.5, 115.5, 113.3, 75.8, 71.4, 71.2. *Anal.* Calcd for $C_{35}H_{26}O_6$: C, 77.48; H, 4.83. Found: C, 77.11; H, 4.88.

2-Benzyloxy-5-formylphenyl 4-benzyloxy-*6H*-benzo[*c*]chromen-1-carboxylate (14): IR ($CHCl_3$) υ_{max} 3028, 3012, 2928, 2855, 1738, 1692, 1607, 1566, 1506, 1479, 1454, 1437, 1421, 1381, 1277, 1259, 1186, 1117, 1088, 1013, 918, 812, 781, 770, 762, 743, 719, 696, 671, 652, 465, 449, 422, 407cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H, ArCHO), 7.73 (dd, *J* = 8.4, 2.0 Hz, 1H, ArH), 7.70 (d, *J* = 2.0 Hz, 1H, ArH), 7.60 (d, *J* = 7.6 Hz, 1H, ArH), 7.54 (d, *J* = 8.4 Hz, 1H, ArH), 7.47-7.15 (m, 13H, ArH), 7.12 (d, *J* = 8.4 Hz, 1H, ArH), 6.84 (d, *J* = 8.4 Hz, 1H, ArH), 5.27 (s, 2H, $ArOCH_2$), 5.24 (s, 2H, $ArOCH_2$), 5.14 (s, 2H, $ArOCH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 190.2, 166.4, 155.9, 151.3, 146.3, 140.9, 136.4, 135.6, 132.1, 130.4, 130.3, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 127.5, 127.4, 127.3, 125.9, 125.1, 124.9, 123.3, 120.2, 113.4, 112.2, 71.1, 71.0, 69.6. EI-MS *m/z*: 542 $[M]^+$. HRMS (EI) Calcd for $C_{35}H_{26}O_6$ $[M]^+$: 542.1729; Found: 542.1728.

Nigricanin (1) from 13

A suspension of **13** (17.2 mg, 0.0317 mmol), Pd/C (6.2 mg), and MeOH (20 mL) was vigorously stirred for 30 min under an H_2 atmosphere. The solid materials were removed by filtration, and the solvent was evaporated to give a residue which was subjected to silica gel column chromatography with AcOEt/hexane (1:1). Colorless prisms of **1** (5.0 mg, 55%) were obtained: mp 218 °C (acetone, decomp.) [lit.,[4] mp 224 °C (acetone, decomp.)]; ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ 7.80 (d, *J* = 8.8 Hz, 1H, ArH), 7.22 (d, *J* = 8.8 Hz, 1H, ArH), 7.20 (d, *J* = 8.4 Hz, 1H, ArH), 7.14 (d, *J* = 8.4 Hz, 1H, ArH), 6.35 (s, 1H, ArCH), 3.58 (s, 3H, OCH_3). ^{13}C-NMR (125 MHz, $(CD_3)_2CO$) δ 160.0, 151.8, 145.6, 138.2, 135.9, 124.8, 123.0, 121.8, 120.4, 119.0, 118.3, 112.9, 112.0, 99.7, 56.0.

4-Benzyloxy-2-iodo-3-methoxymethoxybenzaldehyde (15)

Under an N_2 atmosphere, *i*-Pr_2NEt (2.7 mL, 15.9 mmol) and MOMCl (1.50 mL, 19.9 mmol) were added to a solution of **9** (4.91 g, 13.9 mmol) in DMF (30 mL) at 0 °C. After stirring for 18 h at 0 °C, 10% HCl aq. (30 mL) was added to acidify the reaction mixture. Water (150 mL) was added to the mixture and extracted with AcOEt. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The resulting yellow residue was subjected to silica gel column chromatography with hexane/AcOEt/$CHCl_3$ (35:1:2 to 5:1:2) to give a yellow solid which was recrystallized from hexane-AcOEt. Colorless needles of **15** (5.40 g, 98%) were obtained: mp 72.8-73.8 °C. IR (KBr) υ_{max} 1275, 1254, 1213, 1200, 1178, 1148, 1126, 1107, 991, 934, 899, 824, 802, 791, 743, 694, 662, 610 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.04 (d, 1H, ArCHO), 7.69 (d, *J* = 8.8 Hz, 1H, ArH), 7.43-7.34 (m, 5H, ArH), 7.03 (d, *J* = 8.8 Hz, 1H, ArH), 5.22 (s, 2H, $ArCH_2Ph$), 5.18 (s, 2H, $ArOCH_2OMe$), 3.61 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.3, 156.4, 146.2, 135.4, 129.5, 128.9, 128.7, 127.7, 127.4, 113.3, 100.9, 99.1, 71.3, 58.7. *Anal.* Calcd for $C_{16}H_{15}IO_4$: C, 48.26; H, 3.80. Found: C, 48.11; H, 3.93.

4-Benzyloxy-2-iodo-3-methoxymethoxybenzoic acid (16)

To a solution of **15** (1.01 g, 2.53 mmol) and 2-methyl-2-butene (11.1 mL, 94.0 mmol) in a mixed solvent of *t*-BuOH, THF, and H_2O (7:6:1, 70 mL), a solution of $NaH_2PO_4{\cdot}2H_2O$ (2.75 g, 17.6 mmol) and $NaClO_2$ (2.65 g, 23.1 mmol) in water (20 mL) was dropwise added and allowed to stand for 3 h. After evaporation of the organic solvent, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a yellow solid. Recrystallization from AcOEt-hexane produced pure **16** (1.02 g, 97%) as colorless prisms, mp 129.2-131.4 °C. IR (KBr) υ_{max} 3062-2789 (br), 2640, 2568, 1685, 1577, 1476, 1462, 1453, 1421, 1404, 1382, 1308, 1274, 1195, 1162, 1082, 1012, 997, 977, 921, 900, 849, 828, 778, 758, 743, 698, 676 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.8 Hz, 1H, ArH), 7.44-7.33 (m, 5H, ArH), 6.98 (d, *J* = 8.8 Hz, 1H, ArH), 5.20 (s, 2H, $ArCH_2Ph$), 5.16 (s, 2H, $ArOCH_2OMe$), 3.61 (s, 3H, OMe). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.1, 147.6, 136.0, 129.6, 129.2, 128.9, 128.0, 113.1, 99.4, 96.1, 71.5, 59.0, 71.5, 59.0. *Anal.* Calcd for $C_{16}H_{15}IO_5$: C, 46.40; H, 3.65. Found: C, 46.29; H, 3.78.

2-Benzyloxy-5-(1,3-dioxolan-2-yl)phenyl 4-benzyloxy-2-iodo-3-methoxymethoxybenzoate (17)

Under an N_2 atmosphere, to a solution of **16** (2.01 g, 4.85 mmol) in CH_2Cl_2 (60 mL), DMAP (151.7 mg, 1.24 mmol), EDC (1.17 g, 6.12 mmol), and **8** (1.10 g, 4.04 mmol) were successively added. The mixture was stirred for 5.5 h at room temperature, poured into ice water, neutralized with sat. $NaHCO_3$ aq., then extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated to give a residue which was subjected to silica gel column chromatography with hexane/AcOEt (6:1 to 2:1) to give a white amorphous solid of **17** (2.69 g, 100%). IR ($CHCl_3$) υ_{max} 3013, 1746, 1580, 1508, 1454, 1381, 1267, 1231, 1202, 1161, 1124, 1082, 966, 793, 770, 750, 712, 698, 675, 467, 449, 434, 411 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 1H, ArH), 7.44-7.23 (m, 12H, ArH), 7.02 (d, *J* = 8.8 Hz, 1H, ArH), 6.91 (d, *J* = 8.4 Hz, 1H, ArH), 5.80 (s, 1H), 5.22 (s, 2H), 5.14 (s, 2H), 5.11 (s, 2H), 4.13-3.97 (m, 4H, $-OCH_2CH_2O-$), 3.62 (s, 3H, OMe). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.0, 154.2, 151.0, 147.1, 140.2, 136.5, 135.7, 131.2, 128.8, 128.7, 128.51, 128.46, 127.9, 127.6, 127.3, 125.2, 121.4, 113.6, 112.8, 103.1, 99.0, 71.1, 70.7, 65.3, 58.6. EI-MS *m/z*: 668 $[M]^+$; HRMS (EI) Calcd for $C_{26}H_{29}IO_8$ $[M]^+$: 668.0907; Found: 668.0910.

3,8-Dibenzyloxy-10-hydroxychromeno[5,4,3-*cde*]chromen-5(10*H*)-one (18)

A mixture of **17** (113.8 mg, 0.17 mmol), $Pd(OAc)_2$ (9.9 mg, 0.0441 mmol), Ag_2CO_3 (91.4 mg, 0.331 mmol), PPh_3 (21.5 mg, 0.0820 mmol), and DMA (3 mL) was stirred for 6 h at 120 °C, then cooled to room temperature. To the mixture, PPTS (384.0 mg, 1.52 mmol) and water (1 mL) was added, and then stirred for 18 h at rt and for 2.5 h at 80 °C. After the mixture was filtered, the filtrate was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated to give a residue which was subjected to silica gel column chromatography with benzene/hexane/AcOEt (10:10:1 to 10:3:1) Colorless prisms of **18** (62.3 mg, 81%) was obtained. When this reaction was carried out using 1.78 g of **17**, the chemical yield was 73%, mp 210.4-212.9 °C ($CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, d, *J* = 8.5 Hz), 7.49-7.30 (10H, m, ArH), 7.19 (2H, t, *J* = 6.0 Hz, ArH), 7.11 (1H, d, *J* = 7.0 Hz, ArH), 6.73 (1H, d, *J* = 5.0 Hz), 5.33 (2H, s, $ArCH_2Ph$), 5.29 (2H, s, $ArCH_2Ph$), 3.48 (1H, d, *J* = 5.0 Hz, OH). HRMS (EI) Calcd for $C_{28}H_{20}O_6$ $[M]^+$: 452.1260; Found: 452.1283. This compound was gradually decomposed.

Nigricanin (1) from 18

A suspension of **18** (50.9 mg, 0.112 mmol), 10% Pd/C (13.5 mg), and MeOH (40 mL) was heated at 90 °C with vigorous stirring for 90 min under an H_2 atmosphere. The solid materials were removed by filtration, and the solvent was evaporated to give a residue which was subjected to silica gel column chromatography using AcOEt/hexane (1:10 to 1:1). Colorless prisms of **1** (29.8 mg, 93%) were obtained. When this reaction was carried out using 365.5 mg of **18**, the chemical yield was 86%.

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