Note

Improved Synthesis of Nigricanin

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An ellagic acid-related natural product, nigricanin (1), was synthesized *via* the Ullmann coupling reaction of 2-bromo-3,4-dialkoxybenzaldehyde (4) followed by the Cannizzaro reaction for desymmetrization of the symmetric biaryl compound (5). Compared to our previously reported study, the presented synthesis improved the sequence step number.

Key words Ullmann coupling; Cannizzaro reaction; ellagic acid; *Russula nigricans*

Nigricanin (**1**) was isolated from fruiting bodies of *Russula nigricans* (Russulaceae), and its chemical structure was determined by Liu and colleagues in 2004.[1] The structural feature of **1** is possessing a highly oxygenated tetracyclic skeleton which is an ellagic acid-like heterocyclic system with partially-reduced aromatic rings. This class of compounds often exhibits interesting biological activities,[2–7] thus their total synthesis would be an attractive subject. Recently, we achieved the synthesis of **1**, in which a palladium-mediated biaryl coupling reaction of the phenyl benzoate derivative[8] was used in the key step[9] (Chart 1).

In Chart 1, nine steps were necessary for completion of the synthesis of **1**, and the expensive palladium reagent was essential for the key coupling process. In order to improve the efficiency of the synthesis, we planned an alternative synthetic route as shown in Chart 2, involving the Ullmann coupling reaction[10,11] and the Cannizzaro reaction.[12] This sequential method for forming non-symmetrical biaryl compounds *via* the Ullmann coupling and the Cannizzaro reaction has been reported by Kobayashi *et al.*,[13] Moore *et al.*,[14] Bringmann *et al.*,[15] and Seitz and colleagues.[16]

According to the retrosynthesis scheme, we selected isovanillin (**2**) as the starting material for the synthesis of nigricanin (**1**), which was transformed into **3** by the *ortho*-selective bromination with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) (Chart 3). The phenolic hydroxyl group of **3** was protected with the benzyl group to afford **4**,[17] then the coupling precursor **4** was subjected to the Ullmann conditions using an excess amount of copper dust to perform the dimerization reaction for producing **5**. The intramolecular Cannizzaro reaction was effective for desymmetrization of the symmetric structure of **5** under alkaline conditions.[18] Transformation of the generated carboxylic acid into a methyl ester **6** using trimethylsilyl (TMS) diazomethane was necessary, otherwise, the oxidation reaction in the next step did not cleanly proceed. The pyridinium dichromate (PDC) oxidation of the benzylic alcohol of **6** was conducted to form the aldehyde **7**. Finally, treatment of **7** with BBr_3 followed by the addition of methanol was successful for forming the target nigricanin (**1**) in a one-pot operation. The obtained material was identical to the sample in hand which we previously prepared.

Consequently, we completed the synthesis of nigricanin (**1**) *via* a different route from the previously reported way. In the presented scheme, the sequence step number was improved (seven steps), and the synthesis without using of an expensive palladium reagent was accomplished, compared to our previous work.

Experimental

General Melting points (mp) were measured using a Yanagimoto micro-melting point hot-plate apparatus and are uncorrected. The IR spectra were recorded using a Shimadzu FTIR-8400 spectrophotometer. The NMR spectra were obtained using a JEOL α-400 instrument with the chemical shifts being reported as δ ppm and the couplings expressed in Hertz (Hz). The elemental analysis was performed using a Thermo Scientific FlashEA1112 analyzer. Electron ionization mass spectra (EI-MS) was obtained using a JEOL JMS-700 instrument. Silica gel column chromatography was carried out using Wako-gel C-200. Copper was treated by the reported method before use.[19]

2-Bromo-3-hydroxy-4-methoxybenzaldehyde (3)[20] To a solution of isovanillin (**2**) (5.0 g, 32.9 mmol) in $CHCl_3$ (1000 mL), DBDMH (5.2 g, 18.2 mmol) was portionwise added, and the mixture was stirred for 9 h at ambient temperature. After the addition of water (300 mL), the organic layer was separated, washed with brine, and dried over $MgSO_4$. The organic solvent was removed *in vacuo* to give a crude material which was purified by recrystallization from AcOEt. The title compound (**3**, 5.8 g, 25.1 mmol, 77%) was obtained as a pale orange powder, mp 200.2–201.0°C (AcOEt) [lit.[15] mp 206–207°C (EtOH)]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.26 (d, 1H, CHO), 7.58 (d, J=8.8 Hz, 1H, ArH), 6.93 (d, J=8.8 Hz, 1H, ArH), 6.07 (s, 1H, OH), 4.01 (s, 3H, OMe).

3-Benzyloxy-2-bromo-4-methoxybenzaldehyde (4)[20] To a solution of **3** (7.65 g, 33.1 mmol) and K_2CO_3 (13.7 g, 99.4 mmol) in *N*,*N*-dimethylformamide (DMF) (100 mL), BnBr (3.7 mL, 33.6 mmol) was added at room temperature (r.t.), and the mixture was stirred for 1 h at 75°C. After cooling, the mixture was acidified to pH 1, then extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give the title compound (**4**, 9.94 g, 30.9 mmol, 94%) as a pale orange solid, mp 78.1–78.9°C [lit.[20] mp 79–81°C]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.27 (s, 1H, CHO), 7.76 (d, J=8.8 Hz, 1H, ArH), 7.35–7.54 (m, 5H, ArH), 6.98 (d, J=8.8 Hz, 1H, ArH), 5.05 (s, 2H, $ArCH_2$), 3.96 (s, 3H, OMe). This material was used for the next step without further purification.

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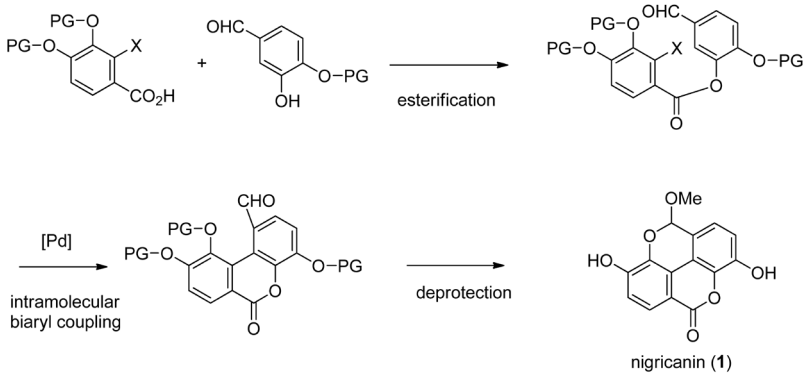

Chart 1. Previous Synthesis of Nigricanin (**1**) *via* Palladium-Mediated Biaryl Coupling Reaction

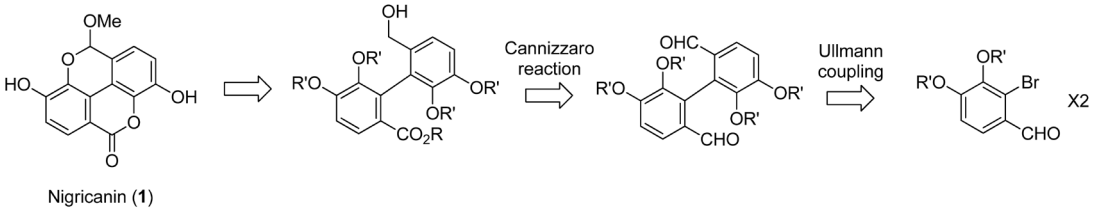

Chart 2. Synthesis Plan for Nigricanin (**1**)

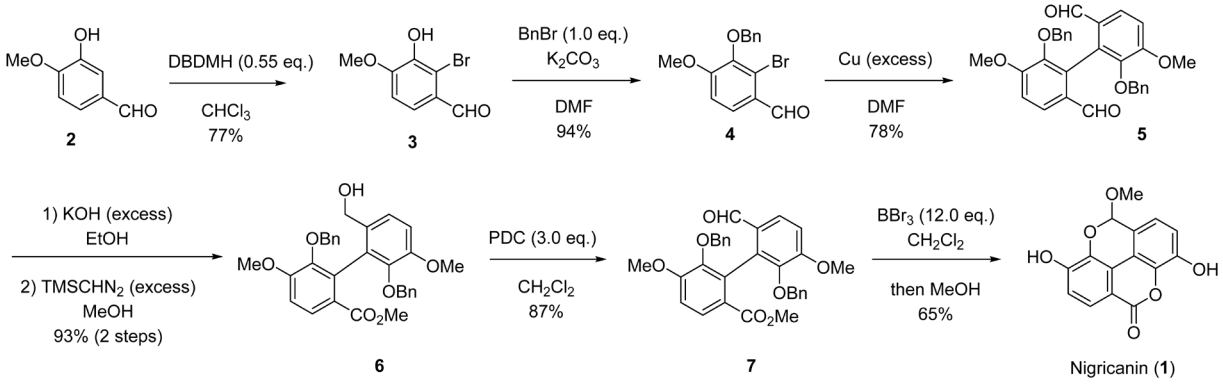

Chart 3. Synthesis of Nigricanin (**1**) *via* Ullmann Coupling and Cannizzaro Reaction

2,2′-Diformyl-5,5′-dimethoxy-6,6′-bis(phenylmethoxy)-biphenyl (5)[21] Under an N_2 atmosphere, a mixture of **4** (2.20 g, 6.85 mmol), Cu (2.61 g, 41.1 mmol), and DMF (10 mL) was stirred for 1 h at 160°C. After cooling, any undissolved materials were removed by filtration, and AcOEt and 10% HCl aq. were added to the mixture for adjusting the pH to 1. The mixture was then extracted with AcOEt, and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crude solid. Recrystallization from AcOEt–hexane gave colorless prisms of **5** (960 mg), and the mother liquid was further purified by silica gel column chromatography with hexane–AcOEt (8 : 1 to 3 : 1) to give **5** (322 mg). Compound **5** (total: 1.28 g, 2.65 mmol, 78%) was obtained in a pure form, mp 126.0–126.5°C (AcOEt/hexane) [lit.[21] mp 123–125°C (MeOH–H_2O 9 : 1)]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.51 (s, 2H, CHO), 7.82 (d, J=8.4 Hz, 2H, ArH), 7.21–6.92 (m, 12H, ArH), 4.77 (s, 4H, $ArCH_2$), 3.99 (s, 6H, OMe). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 56.2, 74.4, 112.0, 126.0, 127.6, 127.8, 128.2, 128.9, 131.9, 137.4, 145.8, 157.8, 190.1.

2-Carbomethoxy-2′-hydroxymethyl-5,5′-dimethoxy-6,6′-bis(phenylmethoxy)biphenyl (6) A mixture of **5** (100 mg, 0.208 mmol), KOH (411 mg, 7.32 mmol), and EtOH (10 mL) was heated at 100°C for 1 h. After cooling to r.t., the mixture was acidified with 10% HCl aq. and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give an amorphous solid (111 mg) which was dissolved in MeOH (1.8 mL). $TMSCHN_2$ (0.34 mL, 0.68 mmol) was added to the solution and the mixture was stirred for 12.5 h at r.t. After concentration to form a residue, silica gel column chromatography with hexane–AcOEt (8 : 1 to 3 : 2) was carried out. The pale yellow oil of **6** (99.0 mg, 0.192 mmol, 93%) was obtained. IR ($CHCl_3$) ν_{max} 3481, 3028, 3009, 2947, 2359, 1720, 1709, 1593, 1570, 1454, 1435, 1271, 1148, 1078, 1026, 752, 698 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, J=9.2 Hz, 1H, ArH), 7.29 (d, J=8.8 Hz, 1H, ArH), 6.86–7.19 (m, 12H, ArH), 4.92 (d, J=11.6 Hz, 1H, $ArCH_2$), 4.83 (d, J=10.6 Hz, 1H, $ArCH_2$), 4.67 (d, J=11.6 Hz, 1H, $ArCH_2$), 4.60 (d, J=10.6 Hz, 1H, $ArCH_2$), 4.29 (dd, A of AB, J=5.6, 11.6 Hz, 1H, $ArCH_2OH$), 4.23 (dd, B of AB, J=5.6, 11.6 Hz, 1H, $ArCH_2OH$), 3.93 (s, 3H, OMe), 3.88 (s, 3H, OMe),

3.64 (s, 3H, CO_2Me), 2.59 (t, J=5.6 Hz, 1H, OH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.3, 156.4, 152.3, 145.6, 144.7, 138.1, 137.2, 133.3, 132.4, 131.2, 128.0 (2C), 127.9 (2C), 127.7 (2C), 127.5 (2C), 127.2 (3C), 125.1, 123.4, 111.8, 110.8, 74.5, 74.0, 63.9, 55.82, 55.76, 51.9. *Anal.* Calcd for $C_{31}H_{30}O_7$: C, 72.36; H, 5.88. Found: C, 72.01; H, 5.82.

2-Carbomethoxy-2′-formyl-5,5′-dimethoxy-6,6′-bis-(phenylmethoxy)biphenyl (7) Under an N_2 atmosphere, to a mixture of PDC (2.09 g, 5.55 mmol) and CH_2Cl_2 (4 mL), a solution of **6** (952.5 mg, 1.85 mmol) in CH_2Cl_2 (18.6 mL) was added at 0°C, and the mixture was stirred at r.t. for 38 h. After Celite™ filtration, the filtrate was concentrated to give a crude solid which was subjected to silica gel column chromatography with hexane–AcOEt (8 : 1 to 3 : 2). The colorless powder of **7** (822.7 mg, 1.61 mmol, 87%) was obtained. mp 134.7–135.5°C (AcOEt/hexane). IR (KBr) ν_{max} 3028, 2945, 2841, 1717, 1684, 1587, 1570, 1431, 1275, 1146, 1020, 741 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.53 (s, 1H, CHO), 7.90 (d, J=8.8 Hz, 1H, ArH), 7.80 (d, J=8.8 Hz, 1H, ArH), 6.90–7.19 (m, 12H, ArH), 4.70–4.87 (m, 4H, $ArCH_2$), 3.952 (s, 3H, OMe), 3.947 (s, 3H, OMe), 3.58 (s, 3H, CO_2Me). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 190.4, 166.1, 157.4, 156.3, 146.0, 144.9, 137.8, 137.3, 135.9, 130.9, 128.2, 127.92 (2C), 127.90 (2C), 127.5, 127.44 (2C), 127.42, 127.36 (2C), 127.3, 125.2, 123.2, 111.2, 111.0, 74.12, 74.09, 55.9, 55.8, 51.7. *Anal.* Calcd for $C_{31}H_{28}O_7$: C, 72.64; H, 5.51. Found: C, 72.76; H, 5.39.

Nigricanin (1)[1,9] Under an N_2 atmosphere, to a solution of **7** (257 mg, 0.501 mmol) in CH_2Cl_2 (25 mL) was added BBr_3 (1 M solution in CH_2Cl_2, 6.0 mL, 6.0 mmol) at 0°C, and the mixture was stirred for 3.5 h at r.t. After cooling to 0°C, the mixture was poured into MeOH and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. To the resulting residue, MeOH (25 mL) was added and the mixture was stirred for 16 h at r.t. Concentration *in vacuo* gave a pale orange solid which was recrystallized from CH_2Cl_2–MeOH to afford the colorless needles of **1** (92.7 mg, 0.324 mmol, 65%), mp 217.4°C (CH_2Cl_2/MeOH, decomp.) [lit.[1] mp 224°C (acetone, decomp.)]. IR (KBr) ν_{max} 3427–3009 (br), 1701, 1603, 1589, 1273, 1236, 1184, 1103, 1080, 953, 910, 818, 721 cm^{-1}. ^{1}H-NMR (400 MHz, acetone-d_6) δ: 7.80 (d, J=8.8 Hz, 1H, ArH), 7.22 (d, J=8.4 Hz, 1H, ArH), 7.20 (d, J=8.8 Hz, 1H, ArH), 7.14 (d, J=8.4 Hz, 1H, ArH), 6.35 (s, 1H, ArCH), 3.58 (s, 3H, OMe). ^{13}C-NMR (100 MHz, acetone-d_6) δ: 160.0, 151.8, 145.6, 138.2, 135.9, 124.8, 123.0, 121.8, 120.3, 119.0, 118.3, 112.9, 112.0, 99.7, 56.0. *Anal.* Calcd for $C_{15}H_{10}O_6$: C, 62.95; H, 3.53. Found: C, 62.87; H, 3.46.

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Conflict of Interest The authors declare no conflict of interest.

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