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TOTAL SYNTHESIS OF UROLITHIN C 3-GLUCURONIDE

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Dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday

Abstract – Urolithin is a metabolite of a class of compounds known as polyphenols which are found in various fruits, including pomegranates, nuts and strawberries. Urolithin is a biologically−active compound which has anti-inflammatory, antioxidant and anticancer properties. Our laboratory has focused on the use of a palladium-catalyzed intramolecular biaryl coupling reaction to yield urolithin C 3-glucuronide (uro-C 3-glur). The total synthesis of uro-C 3-glur has been accomplished in 11 steps starting from the commercially available 3,4-dimethoxybenzaldehyde. We now report full details of the total synthesis of urolithin C 3-glucuronide (**1**).

Over recent years, it has been reported that gastrointestinal microbiota metabolize xenobiotics, which are produced from natural products,[1] i.e., urolithins, which are hydroxylated dibenzo[*b*,*d*]pyran-6-one derivatives, contain urolithin A (uro-A), urolithin B (uro-B), urolithin C (uro-C) and urolithin D (uro-D) derivatives which are produced *in vivo* by the gastrointestinal microbiota of humans and different animals upon intaking ellagitannins (ETs), which are high molecular weight polyphenols and ellagic acids (EAs)[2-7] (Figure). There are many different phenolic antioxidants, such as ETs and EAs, in walnuts and pomegranates, which have been linked to potential preventive effects against chronic diseases like

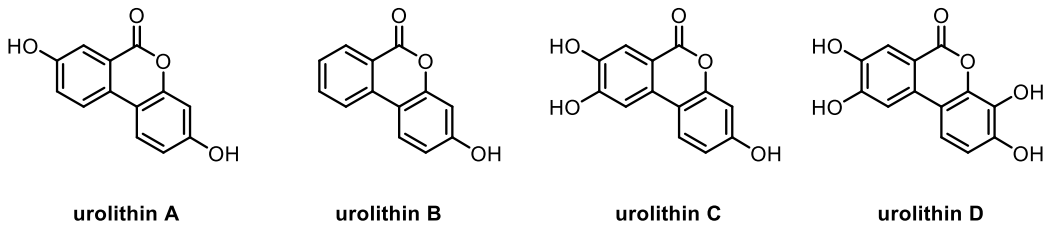
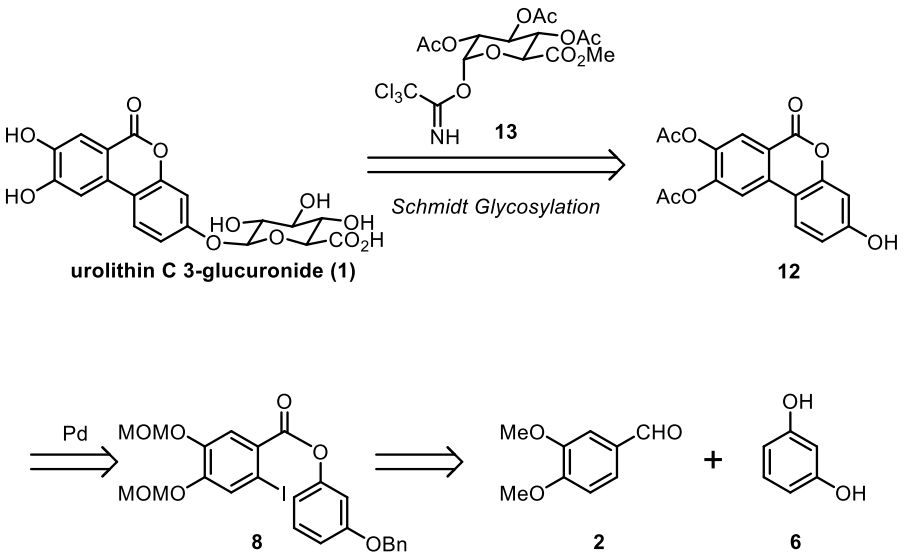


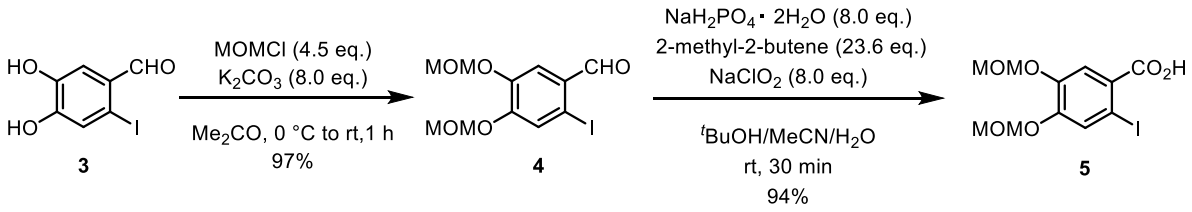
Figure. Structures of urolithins A-D

diabetes, cancer, cardiovascular diseases, and neurodegenerative diseases.[8,9] The bioavailability of ETs and EAs are much lower than the transformed urolithins. The glucuronides of uro-A, uro-B, uro-C and sulfate conjugates are formed by the urolithins which circulate in the plasma. The total concentrations of these metabolites can reach to the range of 0.2-20 μM.[6,8] Although it is suggested that there are positive health effects arising from the metabolism of ETs, there is not enough *in vivo* research. Thus, a clear evaluation in terms of the *in vivo* biological effects of these metabolites is necessary.[6,8] In addition to these reports, it has been shown that phase Ⅱ metabolites of the urolithins, which are primarily glucuronide and sulfate conjugates, can reach systemic human tissues.[10] In recent years, research regarding urolithins has concentrated on the phase Ⅰ metabolites which are mainly composed of uro-A and uro-B, whereas we have been interested in the phase Ⅱ metabolites of urolithins. Uro-A glucuronide (uro-A glur) and uro-B glucuronide (uro-B glur) have already been chemically synthesized and purified.[11-13] On the other hand, the chemical synthesis of Uro-C 3-glur has not been completed and the bioavailability of uro-A glur and uro-B glur has been shown to be much greater than that of uro-C 3-glur.[6,14] Thus, we have decided to synthesize urolithin C 3-glucuronide which is needed to provide the advantageous health effects. Our retrosynthetic analysis to form uro-C 3-glur is outlined in Scheme 1. First, we aimed at forming the 6*H*-dibenzo[*b*,*d*]pyran-6-one skeleton of urolithin as an intermediate using a palladium catalyst so that the final product can be generated *via* a Schmidt glycosylation.[14-16] Secondly, we assumed that the precursor of the coupling compound could be derived from the commercially available starting materials, i.e., 3,4-dimethoxybenzaldehyde and resorcinol.



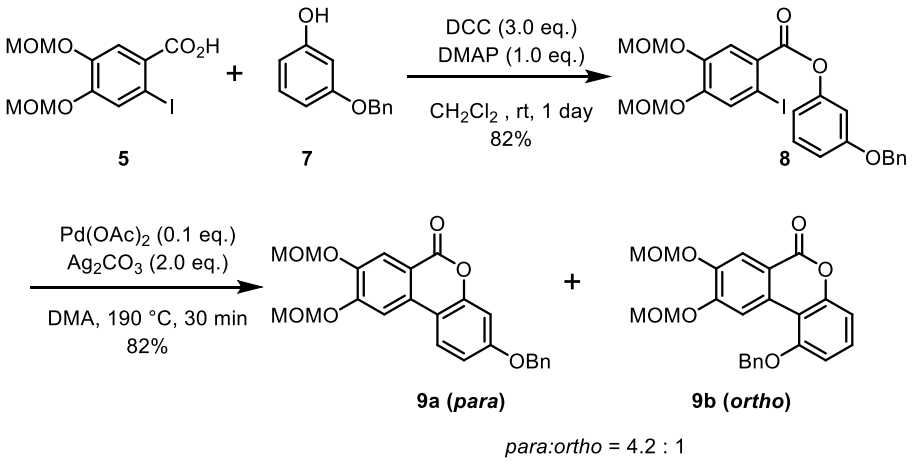
Scheme 1. Synthesis plan of urolithin C 3-glucronide (uro-C 3-glur) (**1**)

According to the retrosynthetic analysis, we chose 3,4-dimethoxybenzaldehyde **2** as the first substrate. The starting material **2** was converted into an iodo compound **3** with reference to the published paper.[17] As depicted in Scheme 2, the iodo compound **3** was transformed into its MOM ether **4**.[18] The substrate **4** was subjected to the Pinnick oxidation to yield a carboxylic acid **5**.[19]



Scheme 2. Synthesis of carboxylic acid **5**

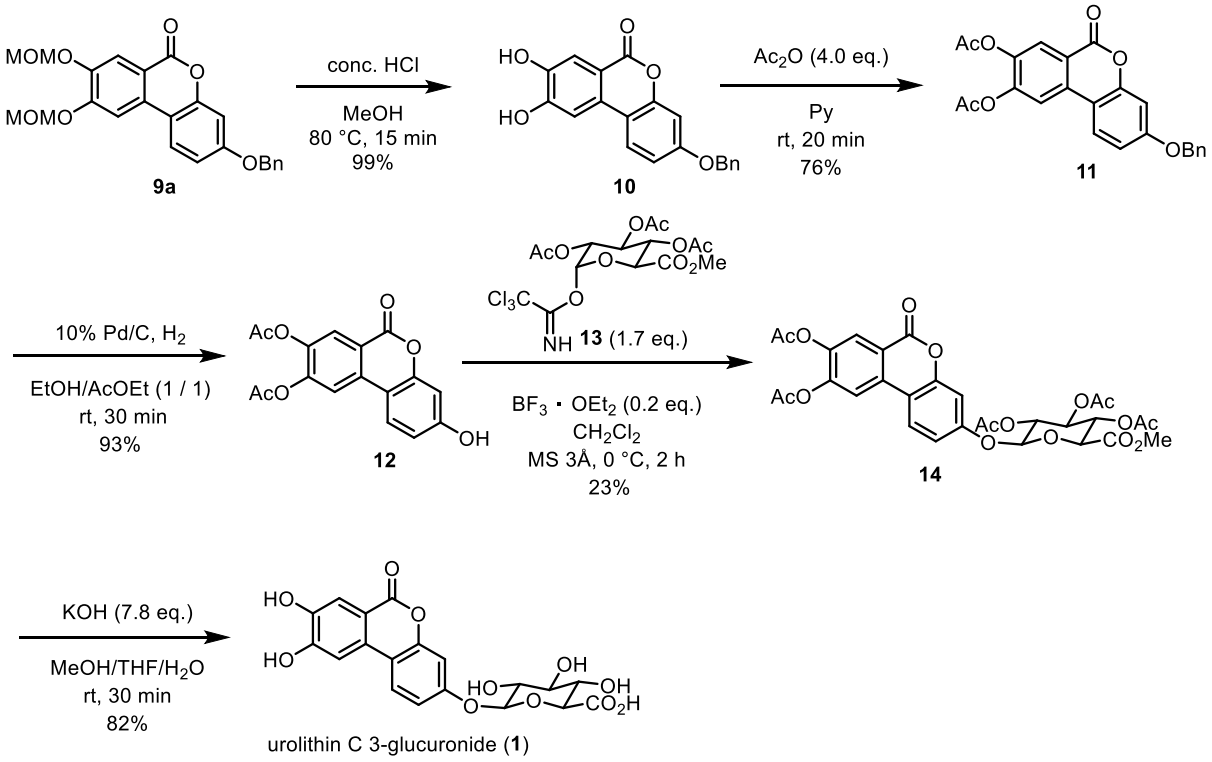
Treating the carboxylic acid **5** with resorcinol monobenzyl ether **7** using *N*,*N*'-dicyclohexylcarbodiimide (DCC) gave the coupling precursor **8** through condensation.[20-23] Exposure of the resulting compound **8** on the use of a palladium-catalyzed intramolecular biaryl coupling reaction afforded a mixture of compound **9a** and its regioisomer **9b** in the ratio of 4.2:1 (Scheme 3).[24-26]



Scheme 3. Intramolecular coupling reaction for **9a** and **9b**

Next, the glucuronic acid derivative was constructed by following a known procedure.[27,28] The desired product **9a** was isolated from the regioisomers (**9a** and **9b**), and these MOM groups were deprotected by concentrated hydrochloric acid (HCl) to give the uro-C derivative **10** in an almost pure form. The resulting compound was reacted with acetic anhydride (Ac_2O) to obtain the protected compound **11**.[29,30] Hydrogenation of compound **11** with 10% Pd/C under H_2 produced the hydroxy compound **12** as a crude mixture.[31] The glycosylation reaction of the compound **12** and the already prepared trichloroacetimidate **13** was performed based on the conditions described in Scheme 4 to produce the precursor **14** of uro-C

3-glur.[8] Finally, the synthesis of urolithin C 3-glucuronide (**1**) was achieved by hydrolysis of the precursor **14** using potassium hydroxide (KOH) in MeOH/THF/H_2O (Scheme 4).[32]



Scheme 4. Synthesis of urolithin C 3-glucronide (uro-C 3-glur) (**1**)

In conclusion, we have established the first chemical total synthesis of urolithin C 3-glucuronide (**1**) from the readily accessible 3,4-dimethoxybenzaldehyde **2** in 11 steps. A key feature of the synthesis is the intramolecular biaryl coupling reaction with a palladium catalyst, which gave a good yield and ratio, in contrast to the yield of the Schmidt glycosylation. Furthermore, we are to improve this yield by optimizing which substrate will suit the reaction better and the operating conditions. We also plan on synthesizing the other urolithins and their related compounds.[33]

EXPERIMENTAL

General: Melting points (mp) were measured with a Yanaco micro melting point apparatus and uncorrected. Analytical TLC was performed on silica gel plates 60 F-254 (Merck Co.) and 60 RP-8 F-254s (Merck KGaA). Silica gel column chromatography was performed using Wako-gel C-200 and reversed-phase column chromatography was carried out with GE Healthcare sephadex^{TM} LH-20. IR spectra were determined in a Shimadzu FTIR-8400 spectrometer. All ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL *a*-400 MHz spectrometer. The chemical shifts were observed in ppm and the

coupling constants were expressed in hertz. Optical rotations were measured on a HORIBA SEPA-500 polarimeter. Electron ionization mass spectra (EI-MS) were recorded using a JEOL JMS-700 instrument.

2-Iodo-4,5-di(methoxymethoxy)benzaldehyde (4)

K_2CO_3 (122 mg, 0.88 mmol) was added to a solution of the substrate **3** (31 mg, 0.11 mmol) in acetone (2 mL), which was stirred until the temperature reached 0 °C under an N_2 atmosphere. MOMCl (0.045 mL, 0.51 mmol) was slowly poured into the mixture over a period of 15 min, while keeping the temperature at 0 °C. After adding all the reagents, the temperature was increased to room temperature. The reaction mixture was stirred for another 1 h at room temperature. The reaction mixture was then quenched with saturated aqueous NH_4Cl at 0 °C and extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and saturated brine (1 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using silica gel column chromatography (hexane/AcOEt = 6:1) to afford **4** (39.8 mg, 97%) as a yellow solid: mp 79.2-80.7 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.68 (s, 1H), 7.66 (s, 1H), 5.31 (s, 2H), 5.27 (s, 2H), 3.53 (s, 3H), 3.50 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.6, 152.6, 147.4, 129.3, 126.1, 116.6, 95.1, 95.0, 93.2, 56.6, 56.4; IR (KBr) 2955, 2360, 1682, 1576, 1414, 1257, 923, 744, 613 cm^{-1}; HRMS (EI) *m/z* [M^+] calcd for $C_{11}H_{13}O_5I$ 351.9808, found 351.9795.

2-Iodo-4,5-di(methoxymethoxy)benzoic acid (5)

To a solution of **4** (9.2 g, 26.1 mmol) in *t*-BuOH (350 mL) and MeCN (85 mL) were added $NaH_2PO_4{\cdot}2H_2O$ (32.7 g, 209 mmol) and 2-methyl-2-butene (64 mL, 601 mmol). The solution was cooled to 0 °C and $NaClO_2$ (19 g, 209 mmol) dissolved in H_2O (175 mL) was slowly added. After stirring for 30 min, AcOEt and H_2O were added. The organic layer was separated and the aqueous layer was extracted with AcOEt (3 × 200 mL). The combined organic layer was washed with saturated brine (1 × 100 mL) and dried over $MgSO_4$. The combined organic layer was filtered and concentrated under reduced pressure. The crude residue was purified by recrystallization from AcOEt to afford **5** (9.0 g, 94%) as a white powder: mp 163.8-165.0 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.77 (s, 1H), 5.28 (s, 2H), 5.26 (s, 2H), 3.52 (s, 6H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 166.8, 149.5, 146.2, 128.3, 126.1, 118.8, 94.8, 94.6, 85.8, 56.6, 55.9; IR (KBr) 2991, 2511, 1693, 1587, 1434, 1330, 1157, 1074, 716 cm^{-1}; HRMS (EI) *m/z* [M^+] calcd for $C_{11}H_{13}O_6I$ 367.9757, found 367.9722.

3-Benzyloxyphenyl 2-iodo-4,5-di(methoxymethoxy)benzoate (8)

5 (2.4 g, 6.5 mmol) and DCC (4.0 g, 19.5 mmol) were dissolved in DCM (25 mL). To the solution, **7** (1.3 g, 6.8 mmol) dissolved in DCM (25 mL) and DMAP (0.79 g, 6.5 mmol) were added, then the mixture

was stirred for 1 day at room temperature. After the reaction, the mixture was filtered, and the solvent was removed in vacuo. The crude residue was purified by silica gel column chromatography (hexane/AcOEt/CH_2Cl_2 = 5:1:1) to afford **8** (2.9 g, 82%) as a yellow solid: mp 61.2-62.2 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.79 (s, 1H), 7.45-7.30 (m, 6H), 6.90-6.85 (m, 3H), 5.30 (s, 2H), 5.28 (s, 2H), 5.07 (s, 2H), 3.53 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.8, 159.7, 151.6, 150.7, 146.7, 136.6, 129.8, 128.6, 128.4, 128.0, 127.5, 126.7, 119.6, 114.2, 112.6, 108.7, 95.4, 95.1, 86.7, 70.2, 60.4, 56.6, 56.5; IR (KBr) 1678, 1284, 976 cm^{-1}; HRMS (EI) *m/z* [M$^+$] calcd for $C_{24}H_{23}O_7I$ 550.0488, found 550.0457.

3-Benzyloxy-8,9-di(methoxymethoxy)-6*H*-dibenzo[*b,d*]pyran-6-one (9a) and 1-benzyloxy-8,9-di(methoxymethoxy)-6*H*-dibenzo[*b,d*]pyran-6-one (9b)

Under an N_2 atmosphere, **8** (1.4 g, 2.54 mmol), Ag_2CO_3 (1.4 g, 5.09 mmol) and $Pd(OAc)_2$ (57.0 mg, 0.25 mmol) were dissolved in DMA (32 mL), then the mixture was stirred at 190 °C for 30 min. After stirring, the reaction mixture was cooled to room temperature and filtered. Water was added to the mixture, and the aqueous layer was extracted with AcOEt (3 × 100 mL). The combined organic layer was washed with water (5 × 20 mL), saturated brine (1 × 20 mL), and dried over $MgSO_4$. The combined organic layer was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (hexane/AcOEt = 4:1) to afford a mixture of **9a** and **9b** (0.88 g, 82%) in the ratio of 4.2:1 as a yellow solid.

Major isomer (9a): White solid: mp 121.7-122.4 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.71 (s, 1H), 7.47-7.33 (m, 5H), 6.99-6.92 (m, 2H), 5.43 (s, 2H), 5.34 (s, 2H), 5.13 (s, 2H), 3.57 (s, 3H), 3.54 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.1, 160.0, 153.6, 152.2, 147.0, 136.1, 131.2, 128.7, 128.3, 127.5, 123.5, 116.1, 114.1, 112.9, 111.3, 106.8, 102.6, 95.4, 95.1, 70.4, 56.6, 56.5; IR (KBr) 1707, 1618, 1501, 1448, 1367, 1331, 1269, 1007 cm^{-1}; HRMS (EI) *m/z* [M$^+$] calcd for $C_{24}H_{22}O_7$ 422.1365, found 422.1361.

Minor isomer (9b): White solid: mp 114.0-114.9 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.09 (s, 1H), 7.55-7.33 (m, 5H), 7.71 (s, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 5.32 (s, 2H), 5.22 (s, 2H), 4.84 (s, 2H), 3.51 (s, 3H), 3.36 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.9, 156.9, 152.4, 152.0, 146.8, 135.8, 130.3, 129.1, 128.8, 128.7, 128.6, 115.9, 115.3, 113.3, 110.6, 108.4, 107.7, 95.1, 94.3, 71.6, 56.6, 56.4; IR (KBr) 1711, 1603, 1506, 1462, 1359, 1283, 1070, 993 cm^{-1}; HRMS (EI) *m/z* [M$^+$] calcd for $C_{24}H_{22}O_7$ 422.1365, found 422.1377.

3-Benzyloxy-8,9-dihydroxy-6*H*-dibenzo[*b,d*]pyran-6-one (10)

9a (210 mg, 0.50 mmol) was dissolved in MeOH (6.6 mL) and concentrated HCl (0.047 mL) was added. The mixture was heated to 80 °C and stirred for 15 min. After reacting, the solvent was removed under

reduced pressure, which gave a solid residue, then it was dissolved in AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and saturated brine (1 × 5 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product **10** (164 mg, 99%) as a white solid which was used without further purification: mp 206.0-206.7 °C; ^{1}H-NMR (400 MHz, acetone-d_6) δ 7.95 (d, J = 8.8 Hz, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.48 (d, J = 7.4 Hz, 2H), 7.39-7.28 (m, 3H), 6.97 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 5.20 (s, 2H); ^{13}C-NMR (100 MHz, acetone-d_6) δ 161.0, 160.7, 153.7, 153.0, 146.8, 137.8, 130.6, 129.5, 129.3, 129.0, 128.5, 124.5, 115.4, 114.8, 113.4, 112.4, 110.8, 107.8, 103.2, 70.9; IR (KBr) 3448, 3354, 1695, 1620, 1578, 1452, 1269, 1170 cm^{-1}; HRMS (EI) *m/z* [M$^+$] calcd for $C_{20}H_{14}O_5$ 334.0841, found 334.0862.

8,9-Diacetoxy-3-benzyloxy-6*H*-dibenzo[*b,d*]pyran-6-one (11)

To a solution of **10** (200 mg, 0.60 mmol) in pyridine (0.8 mL), Ac_2O (0.22 mL, 2.4 mmol) was added. The reaction mixture was stirred at room temperature for 20 min and water was subsequently poured into the reaction mixture. The aqueous phase was acidified to pH 2 and extracted with AcOEt (3 × 3 mL). The combined organic phase was washed with 0.1 M HCl (3 × 3 mL), saturated brine (1 × 3 mL), and dried over $MgSO_4$. The combined organic phase was filtered and concentrated under reduced pressure. The crude residue was purified by recrystallization from AcOEt to afford **11** (190 mg, 76%) as a white solid: mp 182.3-183.0 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.84-7.81 (m, 2H), 7.46-7.34 (m, 5H), 7.00-6.93 (m, 2H), 5.14 (s, 2H), 2.37 (s, 3H), 2.35 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.9, 167.5, 161.0, 160.1, 152.6, 148.1, 141.7, 135.9, 134.4, 128.7, 128.3, 127.6, 125.4, 124.0, 118.2, 116.2, 113.3, 110.4, 102.7, 70.5, 20.8, 20.5; IR (KBr) 1736, 1620 cm^{-1}; HRMS (EI) *m/z* [M$^+$] calcd for $C_{24}H_{18}O_7$ 418.1052, found 418.1058.

8,9-Diacetoxy-3-hydroxy-6*H*-dibenzo[*b,d*]pyran-6-one (12)

To a solution of **11** (174 mg, 0.41 mmol) in EtOH/AcOEt (3.6 mL/3.6 mL), 10% Pd-C (112 mg) was added. Under an H_2 atmosphere, the reaction mixture was stirred at room temperature for 30 min and hydrogenated. The mixture was filtered to remove the catalyst, then concentrated under reduced pressure to afford the crude product **12** (126 mg, 93%) as a white solid which was used without further purification: mp 180.9-182.7 °C; ^{1}H-NMR (400 MHz, acetone-d_6) δ 8.08 (dd, J = 12.4 Hz, J = 8.8 Hz, 3H), 6.92 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 6.82 (d, J = 2.8 Hz, 1H), 2.36 (s, 3H), 2.35 (s, 3H); ^{13}C-NMR (100 MHz, acetone-d_6) δ 132.4, 130.1, 128.8, 68.2, 38.7, 30.9, 30.3, 29.7, 28.9, 23.7, 23.0, 14.0, 10.9; IR (KBr) 3398, 1705, 1622, 1452, 1371.3, 1200, 923 cm^{-1}; HRMS (EI) *m/z* [M$^+$] calcd for $C_{17}H_{12}O_7$ 328.0583, found 328.0577.

Urolithin C 3-(2,3,4-tri-*O*-acetylglucuronide) methyl ester (14)

Under an N_2 atmosphere, to a solution of **12** (115 mg, 0.35 mmol), MS 3Å (150 mg) and trichloroacetimidate **13** (290 mg, 0.59 mmol) in anhydrous DCM (7 mL) at 0 °C, $BF_3{\cdot}OEt_2$ (0.07 mmol) was added. After 2 h, the reaction mixture was quenched with NEt_3 and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (hexane/AcOEt = 3:1 to 1:1) to afford **14** (48.3 mg, 23%) as a white solid: mp 219.7-220.6 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.87-7.83 (m, 2H), 6.99 (dd, *J* = 7.8 Hz, *J* = 2.0 Hz, 2H), 5.39-5.24 (m, 4H), 4.24 (q, *J* = 3.2 Hz, 1H) 3.75 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H), 2.08 (d, *J* = 8.4 Hz, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.0, 169.3, 167.5, 166.6, 159.7, 158.3, 152.2, 148.2, 142.2, 133.8, 125.6, 124.2, 118.6, 116.6, 114.5, 112.6, 105.1, 98.5, 72.7, 71.6, 70.8, 68.9, 53.1, 20.8, 20.6, 20.5; IR (KBr) 1757, 1620, 1572, 1493, 1251, 1173, 1043 cm^{-1}; $[\alpha]_D^{25.1}$ -35.1 (*c* 0.5, $CHCl_3$); HRMS (EI) *m/z* [M^+] calcd for $C_{30}H_{28}O_{16}$ 644.1377, found 644.1343.

Urolithin C 3-glucuronide (1)

14 (20 mg, 0.03 mmol) was dissolved in MeOH/THF/H_2O (0.25 mL/0.5 mL/0.25 mL), and KOH (13.5 mg, 0.24 mmol) was added to the solution, then the reaction mixture was stirred at room temperature for 30 min. The mixture was quenched with Amberlite to pH 4, filtered and concentrated under reduced pressure. The crude residue was purified by reversed-phase column chromatography (MeOH/H_2O = 1:9) to afford **1** (11.6 mg, 82%) as a brown solid: mp 179.0-179.6 °C; ^{1}H-NMR (400 MHz, MeOH-d_4) δ 7.89 (d, *J* = 8.8 Hz, 1H), 7.56 (s, 1H), 7.42 (s, 1H), 7.08-7.01 (m, 2H), 5.09 (dd, *J* = 5.6 Hz, 2.0 Hz, 1H), 4.07 (d, *J* = 9.6 Hz, 1H), 3.66-3.51 (m, 3H); ^{13}C-NMR (100 MHz, MeOH-d_4) δ 161.9, 158.2, 153.6, 151.4, 146.6, 129.5, 123.2, 114.1, 113.6, 113.2, 111.9, 106.6, 104.5, 100.8, 76.0, 73.2, 71.7, 29.4; IR (KBr) 3321, 1718, 1620, 1506, 1267, 1038 cm^{-1}; HRMS (EI) *m/z* [M^+] calcd for $C_{19}H_{16}O_{11}$ 420.0693, found 420.0705.

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33 For the efficient synthesis of urolithin A glucuronide, the manuscript is currently in preparation.