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Skeletal Reorganization: Synthesis of Diptoindonesin G from Pauciflorol F

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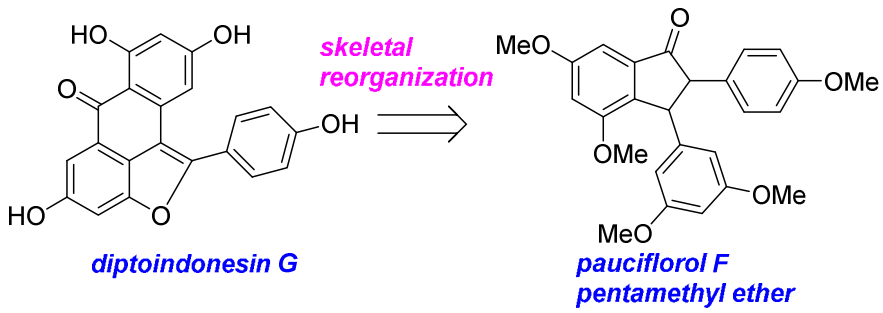


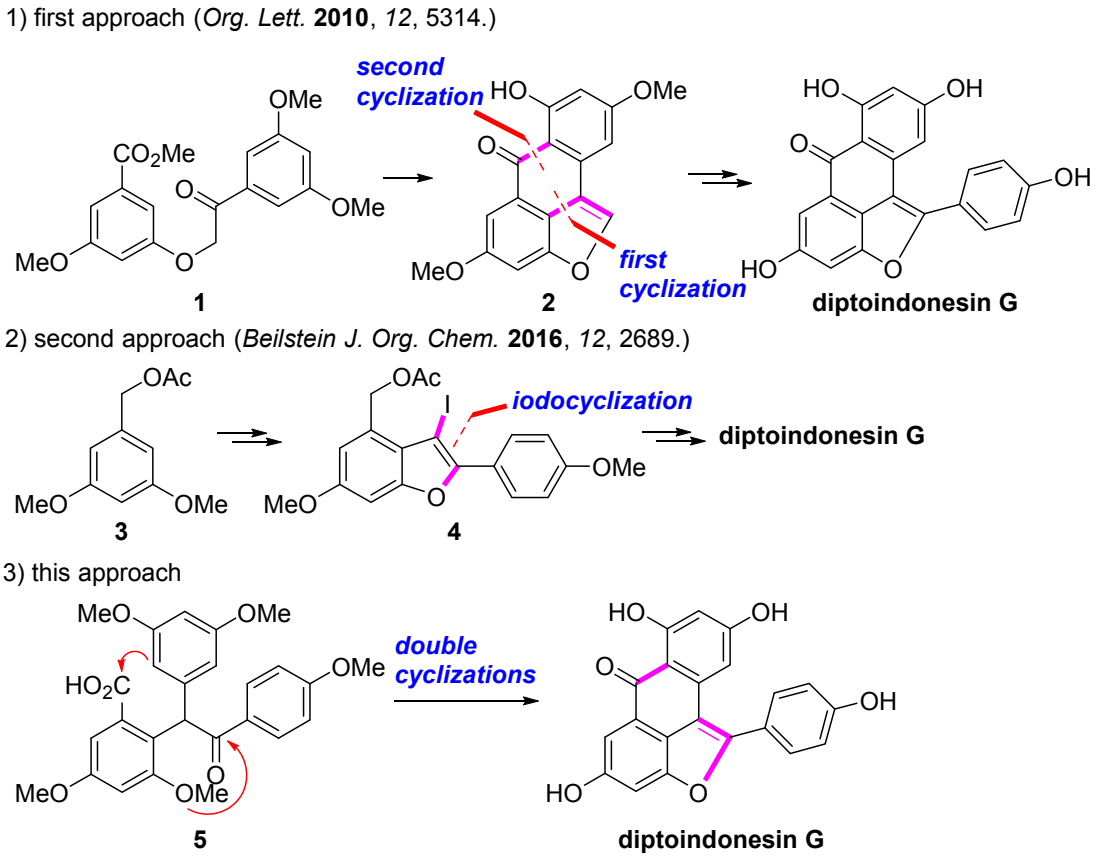
Abstract: Described herein is a novel synthetic approach to diptoindonesin G, a highly potent anticancer oligostilbenoid natural product, from pauciflorol F pentamethyl ether through a skeletal reorganization strategy where oxidative cleavage of the indanone ring system of pauciflorol F and sequential cyclization of the key intermediate allowed direct access to the target skeleton.

Keywords: Diptoindonesin G; Oligostilbenoid; Natural product; Cyclization; Intramolecular

reaction; Cyclodehydration; Friedel-Crafts acylation.

Since its first report on isolation and cytotoxic activity in 2009 by Syah and coworkers,[1] diptoindonesin G, a compact tetracyclic natural products, has been a subject of several investigations for further biological evaluation.[2] After our first total synthesis of this natural product,[3] alternative synthetic approaches were reported by ours[4] and the Tang group.[5]

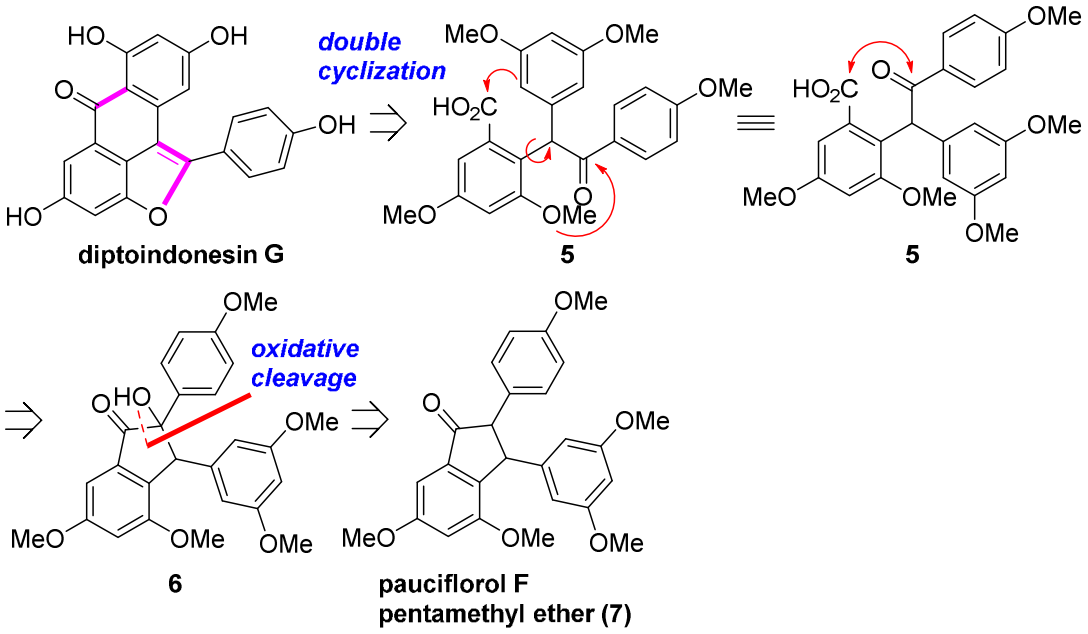
Scheme 1. Our Synthetic Approaches to Diptoindonesin G



As shown in Scheme 1, our first approach to this natural product relied on a domino reaction where cyclodehydration of **1** followed by intramolecular Friedel-Crafts acylation enables construction of tetracyclic product **2** in a one-pot fashion. Recognition of the local symmetry

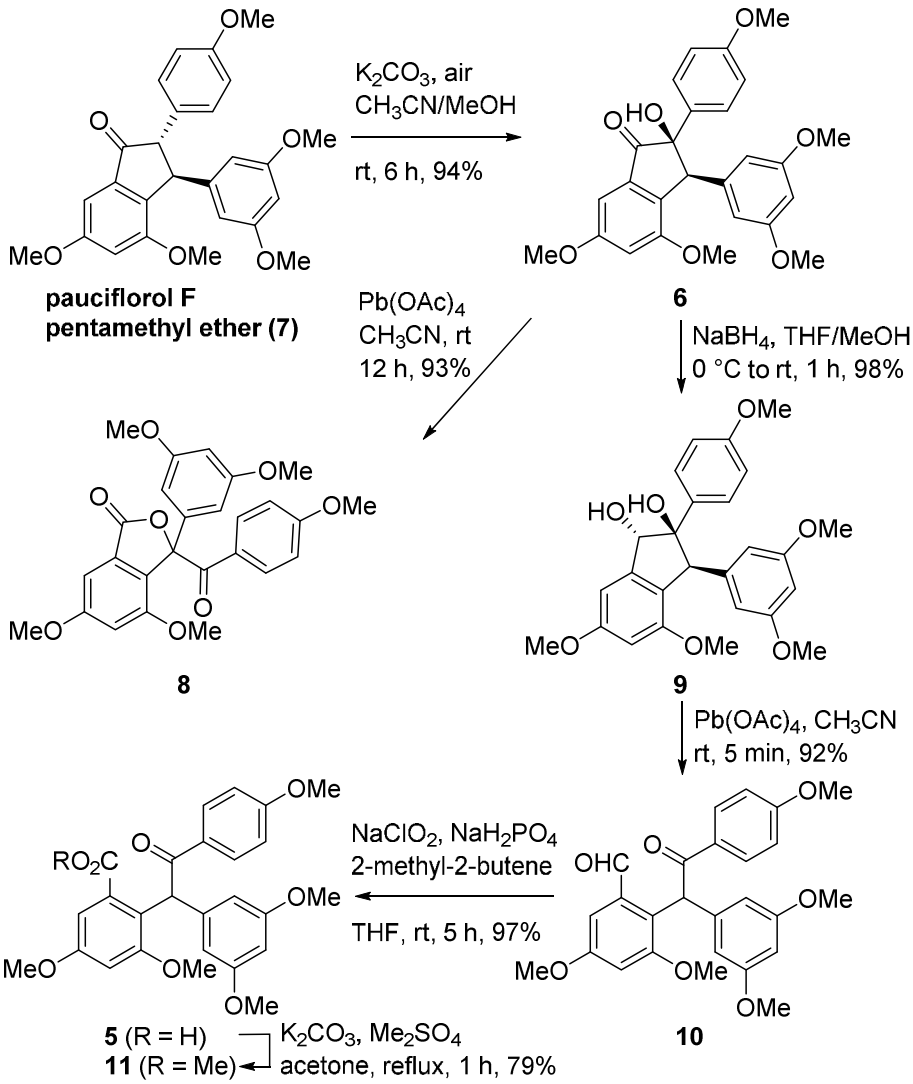
element in the target molecule led us to use a symmetry-driven approach in our second paper. Our new route to this compound began with the notion that **5** would be a viable intermediate as two independent ring closures (as shown in red arrows) of **5** would assemble the target skeleton. Our retrosynthetic analysis of diptoindonesin G is depicted in Scheme 2. Double annulations (cyclodehydration and intramolecular Friedel-Crafts acylation) of **5** would lead to the target molecule, diptoindonesin G. Recognition of the 1,5-dicarbonyl relationship in **5** inspired us to employ oxidative cleavage of **6** to get access to **5**. α-Hydroxyketone **6** was envisioned to stem from pauciflorol F type compound via α-hydroxylation. Overall, through this study we wished to demonstrate that one natural product could be converted to another natural product with different carbon framework through bond reorganization processes.[6]

Scheme 2. Retrosynthetic Analysis



To test the feasibility of our idea, we first synthesized permethylated pauciflorol F **(7)** by following the literature procedures.[7] As shown in Scheme 3, α-hydroxylation of ketone **7** in the presence of K_2CO_3 and air furnished **6**[8] in 94% yield.[9]

Scheme 3. Synthesis of 5 and 11

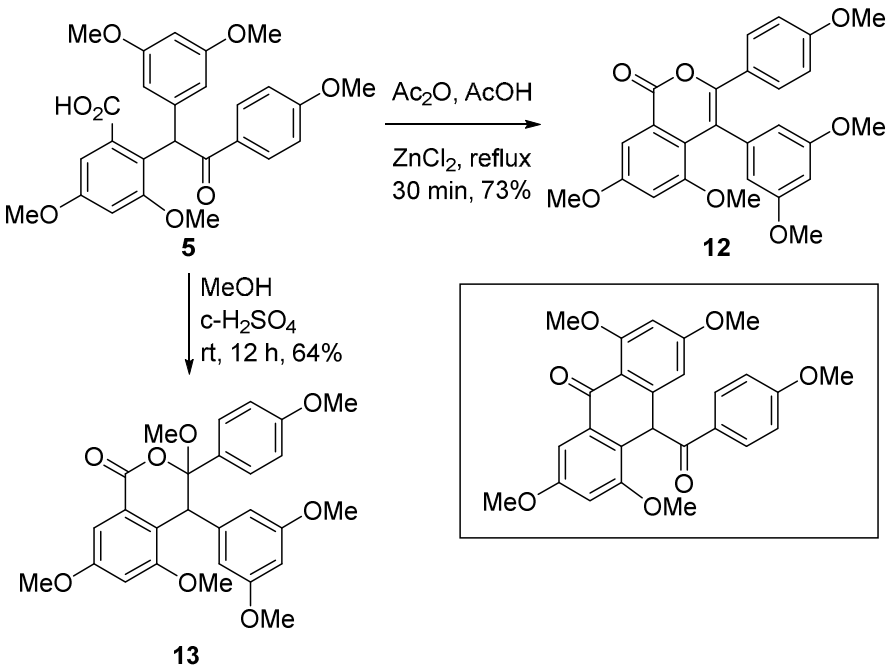


Oxidative cleavage of α-hydroxyketone **6** was first attempted as it would directly give rise to the desired ketocarboxylic acid **5**. While no reaction was observed under periodate-mediated oxidation conditions, exposure of **6** to $Pb(OAc)_4$ (3 equiv)[10] gave lactone **8** instead of **5**. The structure of **8** (crystallized from CH_2Cl_2/hexanes) was firmly established by X-ray crystallographic analysis.[11,12] Formation of **8** can be accounted for as initial generation of carboxylate radical and subsequent 1,5-hydrogen atom transfer.[13] On the other hand, trans-

diol **9**[8] formed as a result of diastereoselective reduction of **6** with $NaBH_4$ was transformed to ketoaldehyde **10** by $Pb(OAc)_4$.[14] Pinnick-Kraus oxidation[15] of **10** proceeded well to give **5** in 97% yield.[16] Acid **5** was converted to its methyl ester **11** under basic conditions.

Having established a reliable route to **5** in hand, we next focused our attention to assemble the two central rings. Initially, intramolecular Friedel-Crafts acylation of **5** was carried out in an attempt to make the anthracene-type compound (shown in the box in Scheme 4). Instead, enol lactone **12** was formed in 73% yield. Similarly, heating **5** in acidic MeOH led to cyclic ketal **13**.

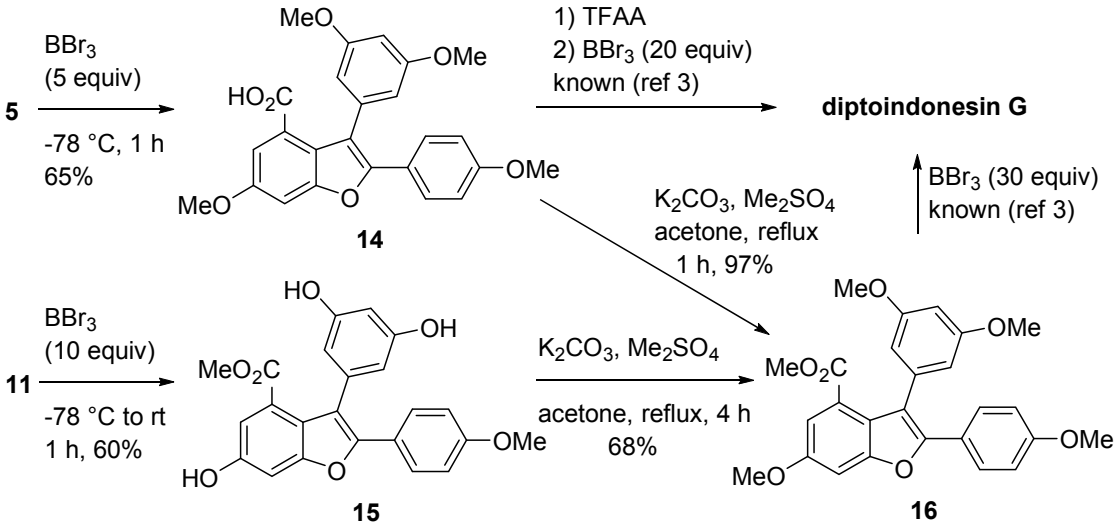
Scheme 4. Cyclization Attempts



From the results described in Scheme 4 as well as our previous experience, we decided to use BBr_3 for milder cyclization (Scheme 5). Exposure of acid **5** to BBr_3 (5 equiv) afforded 65% of benzofuran **14** along with enol lactone **12** in 19% yield as a minor product. Benzofuran **14** was converted to diptoindonesin G by the known two-step procedures (intramolecular

Friedel-Crafts acylation and global demethylation).[3] Increasing the amount of BBr_3 did not result in second cyclization leading to diptoindonesin G; only further demethylation took place, implying demethylation is faster than the intramolecular Friedel-Crafts type acylation.[17] Esterification of **14** gave 97% yield of **16**, which is also a known intermediate for the synthesis of diptoindonesin G.[3] Interestingly, when ester **11** was subjected to the similar reaction conditions, ester **15** was obtained as a major product.[18] A small amount (10~15%) of diptoindonesin G was isolated along with very polar complex mixture[19] upon treatment of **11** with a large excess BBr_3 (30 equiv, -78 °C to rt for 16 h). Ester **15** was also converted to the known **16** under basic conditions. Notably, diptoindonesin G was produced from **16** in an excellent yield by BBr_3.[3] The different reactivity of **14** and **16** for the second cyclization in the presence of BBr_3 indicated that cyclization of ester **16** is faster than that of acid **14**. Although one-pot double cyclization reaction was observed as a minor event with **11**, preferential formation of benzofurans **14** and **15** via facile cyclodehydration enabled us to reach the target molecule with a couple of known synthetic operations.

Scheme 5. Cyclization of 5 and 11



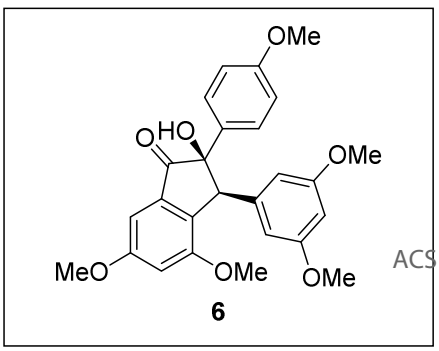
In conclusion, we have developed a new synthetic route to diptoindonesin G, a potent anticancer natural product, from pentamethyl ether of pauciflorol F based on a skeletal reorganization strategy through oxidative ring opening and sequential ring closure as a means to construct the central two ring systems of the target molecule.[20] Extension of oxidative ring cleavage-cyclization protocol for the synthesis of other carbo- and heterocycles is currently underway and the results will be reported in due course.

Experimental Section

General Methods

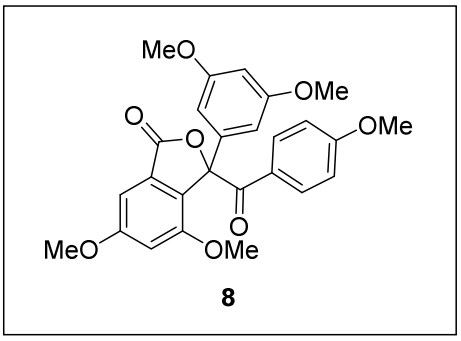
Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. "Concentrated" refers to the removal of volatile solvents via distillation using a rotary evaporator. "Dried" refers to pouring onto, or passing through, anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230−400 mesh) with hexanes, ethyl acetate, and dichloromethane as eluent. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualized with UV light. Melting points were measured using a capillary melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. HRMS were measured with electrospray ionization (ESI) and Q-TOF mass analyzer.

3-(3,5-Dimethoxyphenyl)-2-hydroxy-4,6-dimethoxy-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one (6): To a stirred solution of



6

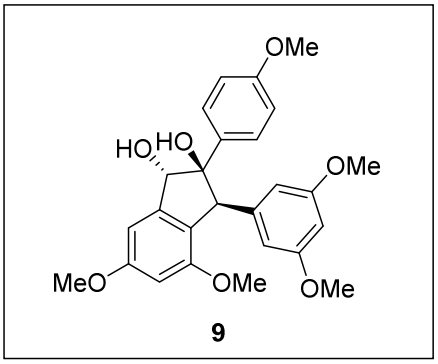
permethylated pauciflorol F **(7)** (310 mg, 0.71 mmol) in acetonitrile/methanol (20 mL, 1:4) was added K_2CO_3 (147.9 mg, 1.07 mmol) at room temperature. After being stirred at rt for 6 h in open air, the reaction mixture was concentrated *in vacuo* to afford the crude product which was purified by flash chromatography on silica gel (hexanes:EtOAc, 4:1) to give **6** as a white solid (302 mg, 94%). mp: 157.6-159.4 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.92 (d, J = 8.4 Hz, 2H), 6.74, (s, 1H), 6.57 (d, J = 8.4 Hz, 2H), 6.07 (s, 1H), 5.82 (br s, 2H), 4.62 (s, 1H), 3.91 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 3.55 (s, 6H), 2.96 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.7, 162.1, 159.9, 158.8, 158.4, 141.8, 137.4, 135.6, 132.5, 128.2, 112.9, 107.5, 107.4, 98.7, 96.9, 85.7, 56.7, 55.9, 55.8, 55.3; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}O_7$ 451.1751, found 451.1755.



8

3-(3,5-Dimethoxyphenyl)-4,6-dimethoxy-3-(4-methoxybenzoyl)isobenzofuran-1(3*H*)-one (8): To a stirred solution of **6** (20 mg, 0.04 mmol) in MeCN (1 mL) was added $Pb(OAc)_4$ (53.2 mg, 0.12 mmol) at room temperature. After being stirred at rt for overnight, the reaction mixture was poured into water (5 mL) and extracted with ethyl acetate (5 mL × 2). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) gave **8** as an off-white solid (18 mg, 93%). mp: 164.2-166.4 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.8 Hz, 2H), 6.93 (s,

1H), 6.81 (d, J = 8.8 Hz, 2H), 6.70 (s, 1H), 6.65 (d, J = 1.2 Hz, 2H), 6.37 (s, 1H), 3.84 (s, 3H), 3.81 (s, 6H), 3.72 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.9, 169.7, 163.7, 163.0, 160.8, 156.7, 138.9, 133.5, 131.7, 126.8, 126.6, 113.6, 106.7, 103.9, 100.7, 99.1, 92.9, 56.1, 56.1, 55.6, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{25}O_8$ 465.1544, found 465.1547.

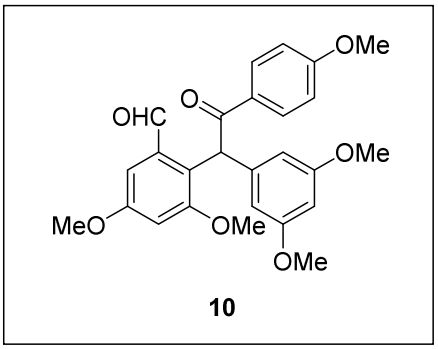


9

(1S,2R,3R)-3-(3,5-Dimethoxyphenyl)-4,6-dimethoxy-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-indene-1,2-diol (9): To a stirred solution of **6** (500 mg, 1.11 mmol) in THF/MeOH (30 mL, 1:2) was added $NaBH_4$ (126 mg, 3.33 mmol) at 0 °C. After being stirred at rt for 1 h, the reaction mixture was quenched with H_2O (20 mL). The mixture was extracted with ethyl acetate (10 mL × 2) and washed with 5% aqueous $NaHCO_3$ (10 mL × 1), brine (10 mL × 1), and H_2O (10 mL × 1), successively. The organic layers were dried over $MgSO_4$ and concentrated to afford the crude product, which on purification by flash chromatography on silica gel (hexanes:EtOAc, 3:2) gave **9** as a colorless gum (491 mg, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.8 Hz, 2H), 6.74 (s, 1H), 6.63 (d, J = 8.8 Hz, 2H), 6.43 (s, 1H), 6.17-6.18 (m, 1H), 5.92-5.93 (d, J = 1.6 Hz, 2H), 5.11 (s, 1H), 4.43 (s, 1H), 3.88 (s, 3H), 3.70 (s, 3H), 3.59 (s, 3H), 3.53 (s, 6H), 2.61 (br s, 1H), 2.22 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.7, 159.7, 158.8, 157.7, 145.9, 141.5, 131.4, 128.6, 120.9, 113.1, 107.7, 99.9, 99.7, 98.9, 89.1, 84.2, 60.1, 55.8, 55.4,

55.3, 55.3; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{29}O_7$ 453.1908, found 453.1904.

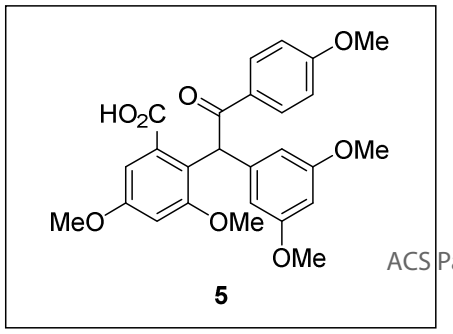
2-(1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethyl)-3,5-dimethoxybenzaldehyde



10

(10): To a stirred solution of **9** (420 mg, 0.93 mmol) in MeCN (20 mL) was added $Pb(OAc)_4$ (412.3 mg, 0.93 mmol) at room temperature. After being stirred for 5 min, the reaction mixture was poured into H_2O (20 mL). The solution was extracted with ethyl acetate (10 mL × 2) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL × 2) and brine (10 mL). The organic layers were dried over $MgSO_4$ and concentrated to give the crude product which was purified by flash chromatography on silica gel (hexanes:EtOAc, 7:3) to give **10** as an off-white solid (384 mg, 92%). mp: 156.2-158.4 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.89 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.30 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.73 (s, 3H), 3.69 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.4, 192.7, 163.3, 160.8, 160.0, 158.5, 142.6, 136.8, 130.9, 130.4, 123.2, 113.7, 107.5, 106.2, 104.5, 98.4, 56.1, 55.7, 55.5, 55.3, 49.2; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}O_7$ 451.1751, found 451.1754.

2-(1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-2-oxoethyl)-3,5-dimethoxybenzoic

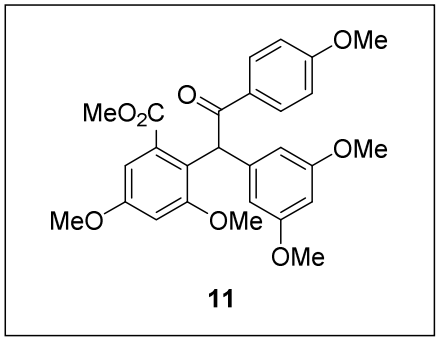


5

acid (5): To a stirred solution of **10** (350 mg, 0.78

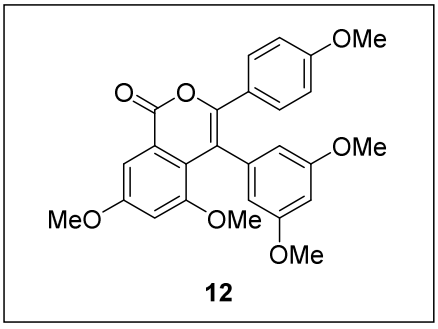
mmol) in a mixture of THF (12 mL) and 2-methyl-2-butene (4 mL) were dropwise added a solution of NaH_2PO_4 (1.07 g, 7.80 mmol) in H_2O (5 mL) and $NaClO_2$ (705 mg, 7.80 mmol) at room temperature. After being stirred for 6 h at rt, the reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate (10 mL), and washed with H_2O (10 mL × 2). The organic layer was dried over $MgSO_4$ and concentrated to afford **5** as a white solid (352 mg, 97%). mp: 160.6-162.4 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.78 (d, J = 8.8 Hz, 2H), 6.87-6.89 (m, 3H), 6.62 (d, J = 2.4 Hz, 1H), 6.60 (s, 1H), 6.33-6.35 (m, 1H), 6.30 (d, J = 2.0 Hz, 2H), 3.74 (s, 6H), 3.67 (s, 6H), 3.50 (s, 3H); .**^{13}C NMR** (100 MHz, DMSO-d_6) δ 196.3, 169.6, 161.9, 159.8, 159.5, 158.9, 157.9, 142.0, 130.2, 129.6, 122.0, 113.2, 107.9, 106.9, 102.2, 97.6, 55.5, 55.3, 55.3, 54.9, 52.4; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}O_8$ 467.1700, found 467.1695.

Methyl 2-(1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)-2-oxoethyl)-3,5-dimethoxybenzoate (11): To a stirred solution of **5** (200 mg, 0.43 mmol) in acetone (5 mL) was added K_2CO_3 (89.8 mg, 0.65 mmol) and dimethyl sulfate (81.6 μL, 0.86 mmol). After being refluxed for 1 h, the reaction mixture was cooled down to rt and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) gave **11** as an off-



11

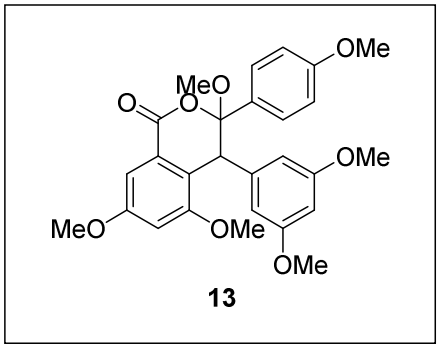
white solid (163 mg, 79%). mp: 146.3-148.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.63 (s, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.35 (d, *J* = 2.0 Hz, 2H), 6.32 (t, *J* = 2.0 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.72 (s, 6H), 3.51 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.4, 168.5, 162.4, 160.3, 159.4, 158.6, 141.6, 131.4, 130.7, 130.3, 123.4, 113.3, 108.2, 107.1, 103.1, 98.6, 55.6, 55.5, 55.4, 55.3, 53.3, 52.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{29}O_8$ 481.1857, found 481.1860.



12

4-(3,5-Dimethoxyphenyl)-5,7-dimethoxy-3-(4-methoxyphenyl)-1*H*-isochromen-1-one (12): To a stirred solution of **5** (20 mg, 0.04 mmol) in AcOH (1 mL) was added acetic anhydride (0.5 mL) and $ZnCl_2$ (1.36 mg, 0.01 mmol). After being refluxed for 30 min, the reaction mixture was cooled down to room temperature, diluted with ethyl acetate (5 mL), and washed with aqueous $NaHCO_3$ (5 mL× 2) and H_2O (5 mL × 2). The organic layer was dried over $MgSO_4$ and concentrated to afford the crude product which was purified by flash chromatography on silica gel (hexanes:EtOAc, 9:1) to give **12** as a colorless gum (14 mg, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.0 Hz, 1H), 7.24-7.26 (m, 2H), 6.68-6.70 (m, 3H), 6.36-6.39 (m, 3H), 3.92 (s, 3H), 3.76 (s, 3H), 3.71 (s, 6H), 3.40 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.6, 160.2, 159.6, 157.6, 148.8,

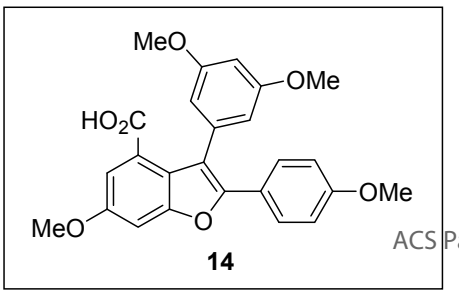
139.9, 130.7, 126.1, 122.7, 122.5, 114.5, 113.2, 109.2, 107.2, 102.2, 99.3, 56.1, 55.9, 55.5, 55.3; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{25}O_7$ 449.1595, found 449.1597.



13

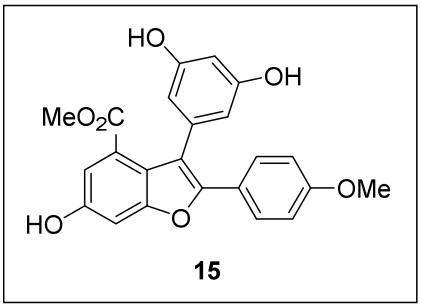
4-(3,5-Dimethoxyphenyl)-3,5,7-trimethoxy-3-(4-methoxyphenyl)isochroman-1-one (13): To a stirred solution of **5** (50 mg, 0.11 mmol) in MeOH (2 mL) was dropwise added c-H_2SO_4 (20 μL). After being stirred at rt for overnight, the reaction mixture was diluted with ethyl acetate (5 mL) and washed with H_2O (5 mL × 2). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) gave **13** as an off-white solid (33 mg, 64%). mp: 174.5-176.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.66 (s, 1H), 6.11 (s, 1H), 5.81 (s, 2H), 4.55 (s, 1H), 3.90 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.52 (s, 6H), 3.16 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.9, 159.9, 159.8, 159.8, 157.4, 139.5, 129.1, 128.4, 125.8, 123.3, 113.4, 108.4, 107.8, 105.2, 103.4, 99.1, 55.9, 55.9, 55.4, 55.2, 51.5, 49.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{29}O_8$ 481.1857, found 481.1852.

3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-



14

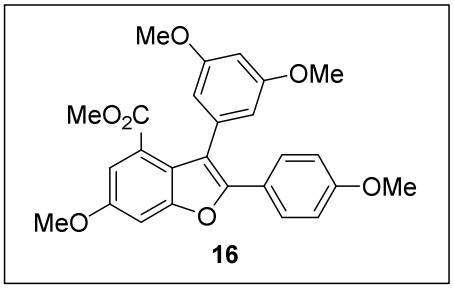
methoxyphenyl)benzofuran-4-carboxylic acid (14): To a stirred solution of **5** (20 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) at -78 °C was dropwise added BBr_3 (0.40 mL, 0.40 mmol). After being stirred at the same temperature for 1 h, the reaction mixture was quenched with cold water, diluted with CH_2Cl_2 (10 mL), and washed with H_2O (10 mL × 2). The organic layers were dried over $MgSO_4$ and concentrated to give the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1 to 1:1) gave **12** (3.3 mg, 17%) and **14** (12 mg, 65%). mp: 202.2-204.5 °C**; ^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.63 (br s, 1H), 7.41-7.45 (m, 3H), 7.08 (br s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.50 (br s, 1H), 6.43 (br s, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 3.70 (s, 6H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 167.4, 160.3, 159.4, 156.8, 154.6, 150.5, 135.4, 127.8, 127.1, 122.3, 120.3, 115.9, 114.1, 111.9, 107.8, 99.6, 98.5, 55.9, 55.2, 55.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{23}O_7$ 435.1438, found 435.1437.



15

Methyl 3-(3,5-dihydroxyphenyl)-2-(4-hydroxyphenyl)-6-methoxybenzofuran-4-carboxylate (15): To a stirred solution of **11** (20 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) under nitrogen atmosphere at -78 °C was dropwise added BBr_3 (0.40 mL, 0.40 mmol). After the addition of BBr_3, the reaction temperature was slowly raised upto room temperature and stirred for 1 h. The reaction mixture was quenched with cold water (2 mL), diluted with ethyl acetate (10 mL), and washed with water (10 mL × 2). The organic layers were dried over

$MgSO_4$ and concentrated to give the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 3:2) furnished **15** as a brown solid (11 mg, 65%). decomposed at 143 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.32 (s, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 1.6 Hz, 1H), 6.98 (d, J = 1.6 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.22-6.24 (m, 1H), 6.10 (d, J = 1.6 Hz, 2H), 3.75 (s, 3H), 3.18 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 167.0, 159.3, 158.8, 154.9, 154.7, 149.8, 135.4, 127.7, 125.2, 122.4, 119.6, 115.9, 114.1, 112.8, 107.4, 101.7, 100.6, 55.2, 51.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{19}O_7$ 407.1125, found 407.1121.



16

Methyl 3-(3,5-dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)benzofuran-4-carboxylate (16).

From compound 14: To a stirred solution of **14** (20 mg, 0.05) in acetone (2 mL) were added K_2CO_3 (11 mg, 0.08 mmol) and dimethyl sulfate (9.5 µL, 0.10 mmol). After being refluxed for 1 h, the reaction mixture was cooled and filtered over a pad of Celite. The filtrate was concentrated to give the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **16** as an off-white solid (20 mg, 97%)**.**

From compound 15: To a stirred solution of **15** (20 mg, 0.05 mmol) in acetone (2 mL) were added K_2CO_3 (31.8 mg, 0.23 mmol) and dimethyl sulfate (28.5 µL, 0.30 mmol). After being

refluxed for 5 h, the reaction mixture was cooled and filtered over a pad of Celite. The filtrate was concentrated to give the crude product. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) provided **16** as an off-white solid (15 mg, 68%). mp: 131.2-132.8 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.2 Hz, 2H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 9.2 Hz, 2H), 6.50 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.77 (s, 6H), 3.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.1, 161.2, 159.7, 157.2, 155.4, 151.8, 136.7, 128.4, 125.3, 123.1, 121.8, 115.8, 113.9, 112.4, 107.6, 100.3, 99.7, 56.2, 55.6, 55.4, 51.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{25}O_7$ 449.1595, found 449.1593.

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Dedication

This paper is dedicated to Professor Deukjoon Kim (Seoul National University) on the occasion of his 70th birthday.

Supporting Information

^{1}H and ^{13}C NMR spectra of synthesized compounds and X-ray crystallographic data for **8**

References and notes

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[9] Use of a catalytic amount of K_2CO_3 as described in Sarpong's paper (ref 8) did not provide the full conversion in our hands. A stoichiometric amount of K_2CO_3 gave **6** in 94% yield.

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[11] See the Supporting Information for details.

[12] CCDC 1582388 contains the supplementary crystallographic data for compound **8**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[16] A pure sample of acid **5** was not obtained despite several purification efforts while the corresponding ester **11** was isolable in a pure form. When the pure ester **11** was hydrolyzed under basic conditions at rt, ^{1}H and ^{13}C NMRs of the resulting acid **5** also showed similar impurity peaks, which might be due to the interaction between neighboring acid and ketone moieties in **5**.

[17] No further cyclization may be due to the insolubility of the polyphenolic compounds produced by the action of BBr_3.

[18] For structural determination of **15**, see the Supporting Information for details.

[19] It seemed that the methyl ester moiety was hydrolyzed under these conditions to give polyphenolic benzoic acid. Ester **16** was isolated in 43% yield by treatment of the crude reaction mixture with K_2CO_3 and dimethyl sulfate.

[20] The known **14** for the synthesis of diptoindonesin G was obtained via acid **5** from pauciflorol F pentamethyl ether **(7)** with 53% overall yield in 5 steps while ester **16** was produced via ester **11** from **7** with 26% overall yield in 7 steps.