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FORMAL TOTAL SYNTHESIS OF AGLAIASTATIN: Pd(0)-MEDIATED CONSTRUCTION OF BENZOFUROCYCLOPENTANE SYSTEM

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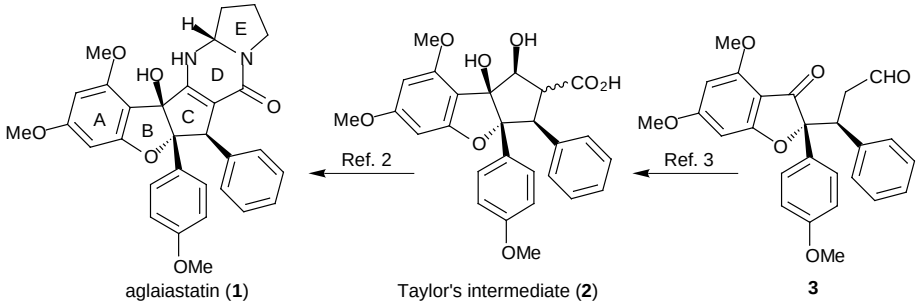
Abstract-Aglaiastatin, an antitumor alkaloid, contains fused pentacyclic system, including a benzofurocyclopentane system and a unique pyrrolopyrimidinone skeleton. In this study, synthesis of a keto aldehyde intermediate, a key intermediate in a previously reported procedure for total synthesis, was accomplished *via* Pd(0)-mediated benzofuran ring closure. Thus, a formal total synthesis of aglaiastatin was achieved.

INTRODUCTION

Aglaiastatin was isolated from the leaves of the tropical plant *Aglaia odorata*; it acts as an agent that induces normal morphology in K-*ras*-transformed fibloblasts.[1] It was found to be a specific inhibitor of protein synthesis, and the alkaloid displayed potent growth inhibition against various tumor cell lines; *e.g.*, its IC_{50} value for K-*ras*-NRK cells was 1.67 ng/mL.[1]

Previously we reported the first total synthesis of aglaiastatin[2] starting from the three fused rings with carboxylic acid (**2**), which was an intermediate in Taylor's total synthesis of rocaglamide.[3] In our synthesis, the crucial pyrrolopyrimidinone ring was constructed by double nucleophilic addition of one nitrogen unit to the acyliminium ion and ketone with concomitant dehydration. Although this method of the synthesis is short and effective, aglaiastatin analogs having various alkyl and aryl groups instead of phenyl and 4-methoxyphenyl groups were difficult to be prepared by this synthetic route. These structurally diverse derivatives will be useful for studying the structure-activity relationship of aglaiastatin-related compounds. Therefore, another convergent synthesis of aglaiastatin was desired. Herein we disclose a formal total synthesis of aglaiastatin by constructing the keto aldehyde (**3**) from which the starting comound of our previous synthesis[2] (**2**) was prepared by Taylor.[3] In the present synthesis, sterically congested

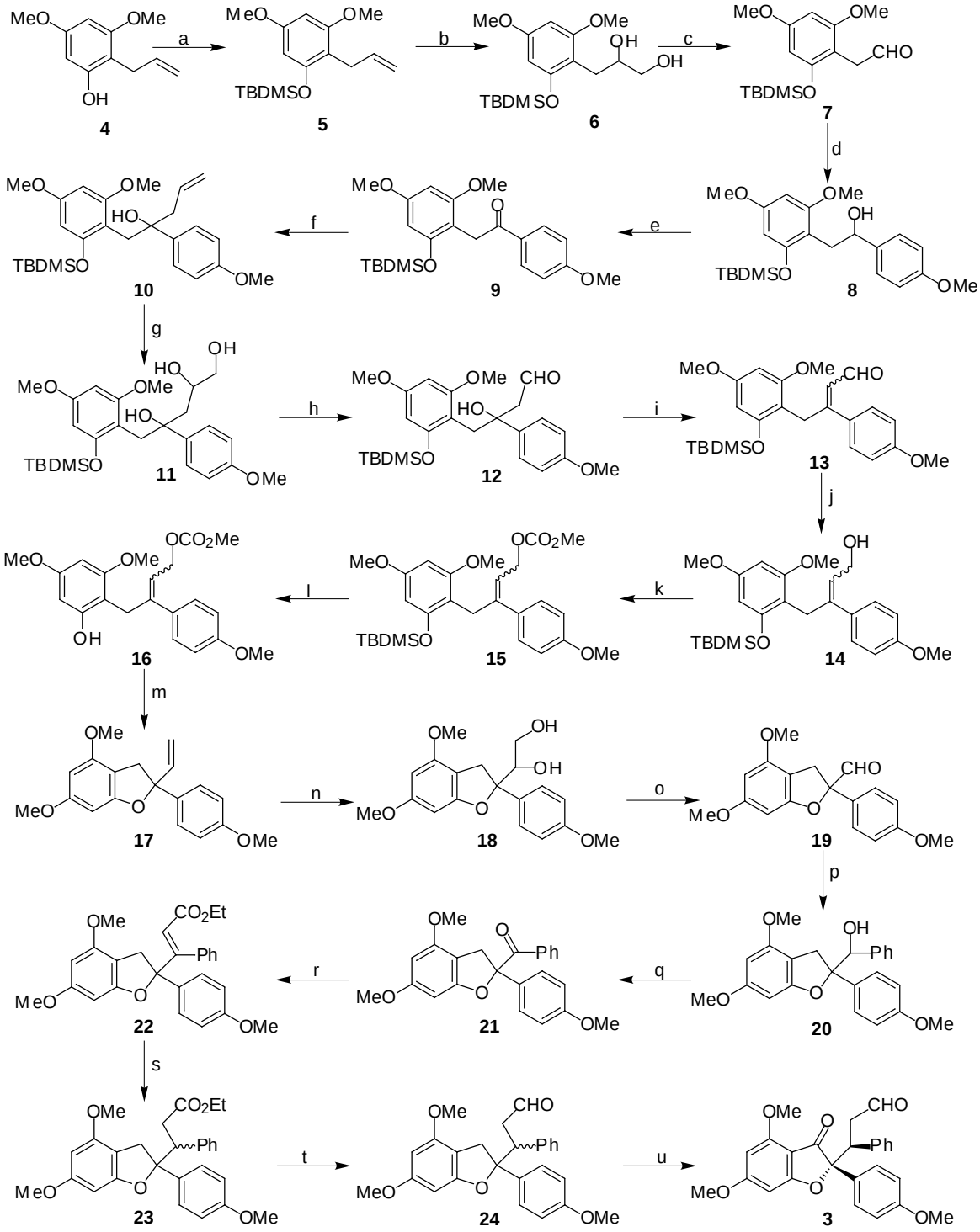
benzofuran-cyclopentane juncture was created by Pd(0)-mediated cyclization. Pd(0)-mediated carbon-carbon bond formation is one of the most important recent topics in organic chemistry.[4] Utility of this class of reactions has been broadened by the synthesis of biologically important compounds effected by asymmetric palladium catalysts.[5] On the other hand, carbon-oxygen bond-forming reaction with Pd(0)[6] is still in its infancy. The present study demonstrated the use of a Pd(0)-mediated reaction to the synthesis of structurally complex natural products.



aglaiastatin (**1**) Taylor's intermediate (**2**) **3**

RESULTS AND DISCUSSION

The synthesis was commenced with protection of a known phloroglucinol derivative (**4**)[7] by a TBDMS group. The double bond of the resulting compound (**5**) was oxidatively cleaved by the standard two-step procedure to give aldehyde (**7)**. The first aryl moiety, a 4-methoxyphenyl group, was introduced by use of the Grignard reagent to afford benzylic alcohol intermediate (**8**) efficiently. The secondary hydroxy group was subjected to tetra-*n*-propylammoium perruthenate (TPAP) oxidation[8] to give ketone (**9**) with no difficulties. The following task was synthesis of substrate (**16**) for the Pd(0)-catalyzed benzofuran ring closure reaction. Attempts to introduce the olefinic moiety of **16** by use of suitably oxygenated Wittig or Wadsworth-Emmons reagents failed. However the following stepwise procedure was successful: homoallylic alcohol (**10**) was obtained by Grignard reaction of **9** with allylmagnesium bromide. In the next, the double bond of **10** was oxidatively cleaved to give aldol (**12**) *via* triol intermediate (**11**). Subsequent dehydration of **12** to **13**, however, was unexpectedly troublesome. Conventional methods using $POCl_3$[9] and $SOCl_2$[10] were unsuccessful. Although Lewis acid ($BF_3{\cdot}Et_2O$)-mediated dehydration[11] afforded a small amount of **13**, the reproducibility of the reaction was inadequate. Finally, we found that refluxing with $CuSO_4{\cdot}3H_2O$[12] in toluene for 15 minutes gave satisfactory results. The *E* /*Z* ratio of the resulting enal was approximately 1:3. Each isomer was separated by silica gel column chromatography. Geometry of the olefins were confirmed by X-Ray crystallographic analysis of an *Z*-**14** derivative, in which the primary alcohol was blocked by *p*-nitrobenzoate, and then, the TBDMS group was removed. Each isomer was independently reduced by DIBALH to afford allylic alcohol (*E*- and *Z*-**14**). The alcohol was converted to carbonate, and the subsequent desilylation by tetra-*n*-butylamminium fluoride (TBAF) gave *E*- and *Z*-**16**. Then, the substrate *Z*-**16** and 5 mol % of $Pd(PPh_3)_4$ were stirred in MeCN at room temperature. As expected, cyclization proceeded smoothly to give desired **17** after 2 hours. Opposite *E*-isomer was also converted to **17** under the same reaction conditions. In the absence of the palladiumreagent, no reaction occurred, indicating that the palladium catalyst was essential for this cyclization. The double bond of the resulting **17** could be utilized for further structural conversion. The vinyl group of **17** was oxidatively cleaved to give aldehyde (**19**) in two steps. Although the succeeding



Scheme 1. Reagents and conditions: (a) TBDMSCl, imidazole/DMF, rt, 1 h, 95%; (b) OsO_4, NMO /aq. THF, rt, 3 h, quant.; (c) $NaIO_4/CH_2Cl_2$-H_2O, 0 °C, 23 h, quant.; (d) 4-MeO-C_6H_4MgBr/THF, -78 °C, 1.5 h, 83%; (e) TPAP, 4-methylmorpholine *N*-oxide (NMO), 4Å molecular sieves (4Å MS), rt, 20 h, 80%; (f) allylmagnesium bromide/THF, -78 °C, 3 h, 96%; (g) OsO_4, NMO/aq. THF, rt 3 h, 97% (diastereomeric mixture); (h) $NaIO_4$/aq. THF, rt, 1 H, 96%; (i) $CuSO_4 \cdot 3H_2O$/toluene, 120 °C, 15 min, 93% (*Z*/*E*=3/1); (j) DIBALH/CH_2Cl_2, -78 °C, 30 min, *Z*-**14** in 99% from *Z*-**13**; 1 h, *E*-**14** in 82% from *E*-**13**; (k) $ClCO_2Me$, pyridine/CH_2Cl_2, 0 °C, 40 min, *Z*- and *E*-**15** in quant. from *Z*- and *E*-**14** respectively; (l) TBAF/THF, 0 °C, 2 h, *Z*-**16** in 95% from *Z*-**15**; 30 min, *E*-**16** in 85% from *E*-**15**; (m) $Pd(PPh_3)_4$/MeCN, rt, 2 h, *Z*-**17** in 95% from *Z*-**16**; 1.5 h, *E*-**17** in 94% from *E*-**16**; (n) OsO_4, NMO/aq. THF, rt, 20 h, quant.; (o) $NaIO_4$/aq. THF, 0 °C, 1 h, 96%; (p) PhMgBr/THF, 0 °C, 30 min, 72% (3:2 diastereomeric mixture); (q) TPAP, NMO, 4Å MS/CH_2Cl_2, rt, 1 h, quant.; (r) $(EtO)_2P(O)CH_2CO_2Et$, NaH/THF, 80 °C, quant.; (s) H_2, 10% Pd/C/AcOEt, rt, 4 h, quant. (7:3 diastereomeric mixture); (t) DIBALH/CH_2Cl_2, -78 °C, 20 min, 92%; (u) DDQ/1,4-dioxane, rt, 40 min, 80% based on the corresponding diastereomer of **24**.

Wadsworth-Emmons reaction afforded the α,β-unsaturated ester, the following introduction of phenyl group by conjugate addition using cupric reagent failed. Instead, the phenyl group was introduced by Grignard reaction with no difficulty to **19** to give **20**. After oxidation of **20** by TPAP, Wadsworth-Emmons reaction gave α,β-unsaturated ester (**22**).

A diastereomeric mixture (7:3) of **23** was obtained by catalytic hydrogenation of **22** on Pd/C. At this stage, the relative stereochemistry of each product was not determined. The subsequent DIBALH reduction and benzylic oxidation by DDQ[13] was conducted without separation of the stereoisomers. Application of DDQ oxidation[13] afforded the desired a sole product in 80% yield. The spectral data of **3** were fully identical to those reported by Taylor.[3] Then, a formal total synthesis of aglaiastatin (**1**) was accomplished, because **3** can be converted to **2** by Taylor's protocol[3] and **2** can be lead to **1** using our synthetic route reported previously.[2] In addition, the main stereoisomers of **23** and **24** were found to have the requisite stereochemistry. Although another stereoisomer was consumed during the final oxidation, the corresponding oxidation product was not detected.

CONCLUSION

A convergent formal total synthesis of aglaiastatin was accomplished *via* Pd(0)-mediated benzofuran formation as a key step. In this route, the two aryl groups are individually introduced by the Grignard reaction. Therefore, this synthetic route is useful for preparation of aglaiastatin derivatives having various structures instead of the two aryl substituents.

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EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and were uncorrected. IR spectra were measured with a Horiba FT-210 spectrophotometer. HRFAB-MS were taken with a JEOL JMS-SX 102. NMR spectra were recorded with a JEOL JNM-EX-400 spectrometer. All reagents and solvents were purified by standard methods. All reactions were carried out under an argon atmosphere unless otherwise stated.

3-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-1-propene (5). A solution of 15.0 g of **4** (76.8 mmol) and 13.6 g of imidazole (0.200 mol) in 100 mL of DMF was stirred for 1 h at rt . Brine was poured onto the reaction mixture, and the mixture was extracted by toluene three times. Combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/3) to give 22.5 g (95%) of **5** as a white powder in yield: mp 35~36 °C. IR (KBr) ν_{max}1606, 1591, 1492, 1464, 1421, 1254, 1209, 1151, 1136, 839 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.13 (1H, d, *J*=2.4 Hz), 6.05 (1H, d, *J*=2.4 Hz), 5.91 (1H, ddt, *J*=17.1, 10.3, 5.9 Hz), 4.92 (1H, ddt, *J*=17.1, 1.8, 1.7 Hz), 4.89 (1H, ddt, *J*=10.3, 1.8, 1.7 Hz), 3.77 (3H, s), 3.75 (3H,

s), 3.30 (2H, dt, *J*=5.9, 1.7 Hz), 1.00 (9H, s), 0.23 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.3, 158.9, 154.7, 137.3, 113.7, 111.5, 97.1, 91.6, 55.7, 55.2, 27.4, 25.8, 18.3, -4.1. HRFABMS (m/z) calcd for $C_{17}H_{29}O_3Si$, 309.1886; found 309.1874 (MH^+).

3-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-1,2-propanediol (6). To a solution of 10.8 g of **5** (34.8 mmol) in 60 mL of THF were successively added 12 mL of 4% aqueous solution of OsO_4 and 6.12 g of NMO (52.2 mmol) at 0 °C. The solution was stirred for 2.5 h at rt. Then, THF was evaporated and the resulting mixture was diluted with H_2O and extracted three times with EtOAc. Combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/1) to give 11.9 g (quantitative) of **6** as a orange oil. IR (neat) ν_{max} 1606, 1589, 1421, 1200, 1149, 1120 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.16 (1H, d, *J*=2.4 Hz), 6.08 (1H, d, *J*=2.4 Hz), 3.90-3.83 (1H, m), 3.81 (3H, s), 3.76 (3H, s), 3.60-3.50 (1H, m), 3.44 (2H, dd, *J*=11.5, 5.6 Hz), 2.90-2.75 (2H, m), 1.02 (9H, s), 0.26 (3H, s), 0.25 (3H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.3, 159.2, 155.1, 109.1, 97.5, 91.8, 72.2, 66.1, 55.7, 55.2, 27.1, 25.3, 18.3, -4.1, -4.1. HRFABMS (m/z) calcd for $C_{17}H_{31}O_5Si$, 343.1941; found 343.1933 (MH^+).

3-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-1-ethanal (7). To a solution of 11.8 g of **6** (34.6 mmol) in 100 mL of CH_2Cl_2 were successively added 50 mL of H_2O and 37.0 g of $NaIO_4$ (0.173 mol) at 0 °C. The resulting heterogeneous mixture was stirred for 9 h. Then, H_2O was added to the mixture, and the mixture was extracted three times with $CHCl_3$. Combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/3) to give 10.7 g (quantitative) of **7** as a orange oil. IR (neat) ν_{max} 1725, 1608, 1591, 1496, 1466, 1421, 1205, 1151, 1120, 837 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.56 (1H, d, *J*=2.0 Hz), 6.16 (1H, d, *J*=2.4 Hz), 6.08 (1H, d, *J*=2.4 Hz) , 3.78 (3H, s), 3.77 (3H, s), 3.57 (2H, d, *J*=2.0 Hz), 0.98 (9H, s), 0.23 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.3, 160.1, 159.5, 155.4, 104.7, 97.2, 91.4, 55.6, 55.3, 38.5, 25.8, 18.2, -4.1. HRFABMS (m/z) calcd for $C_{16}H_{27}O_4Si$, 311.1679; found 311.1677 (MH^+).

3-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-1-ethanol (8). 4-Methoxyphenylmagnesium bromide was prepared from 19.1 g of 4-bromoanisole (0.220 mol) and 7.52 g of magnesium (0.309 mol) in 50 mL of THF. To the resulting solution of Grignard reagent was added a solution of 15.8 g of **7** (50.9 mmol) in 100 mL of THF dropwise at -78 °C. The solution was stirred for 1.5 h at -78 °C. Then, the reaction mixture was diluted with EtOAc. The organic layer was washed with saturated ammonium chloride solution and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/6) to give 17.7 g (84%) of **8** as a white powder: mp 65~68 °C ($CHCl_3$). IR (KBr) ν_{max} 1608, 1589, 1512, 1464, 1419, 1246, 1201, 1173, 1149, 1117, 1103, 835 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (2H, m), 6.90-6.80 (2H, m), 6.15 (1H, d, *J*=2.5 Hz), 6.08 (1H, d, *J*=2.4 Hz), 4.80 (1H, dd, *J*=8.4, 4.5 Hz), 3.80 (3H, s), 3.77 (3H, s), 3.76 (3H, s), 3.00 (1H, dd, *J*=13.7, 4.5 Hz), 2.95 (1H, dd, *J*=13.7, 8.4 Hz), 1.03

(9H, s), 0.27 (3H, s), 0.25 (3H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.4, 159.3, 158.6, 155.2, 137.5, 126.8, 113.4, 110.0, 97.3, 91.7, 74.3, 55.6, 55.2, 33.9, 25.9, 18.3, -3.9, -4.1. HRFABMS (m/z) calcd for $C_{23}H_{35}O_5Si$, 419.2254; found 419.2283 (MH^+).

3-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-1-ethanone (9). To a solution of 67.3 g of **8** (0.161 mol) in 500 mL of CH_2Cl_2 were successively added 2.82 g of tetra-*n*-propylammonium perruthenate (TPAP, 8.02 mmol), 28.3 g of NMO (0.242 mol), and 60 g of 4Å MS at 0 °C. The mixture was stirred for 20 h at rt. Then, insoluble materials of the mixture were filtered off through celite and the resulting filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/6) to give 53.6 g (80%) of **9** as a white powder: mp 155~157 °C ($CHCl_3$). IR (KBr) ν_{max} 1680, 1599, 1500, 1466, 1431, 1267, 1203, 1153, 1107, 991, 839, 823 cm^{-1}.^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05-7.95 (2H, m), 6.95-6.85 (2H, m), 6.15-6.10 (1H, m), 6.08 (1H, d, *J*=2.4 Hz), 6.10-6.05 (1H, m), 4.12 (2H, s), 3.86 (3H, s), 3.77 (3H, s), 3.70 (3H, s), 3.00 (1H, dd, *J*=13.7, 4.5 Hz), 0.89 (9H, s), 0.19 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 196.4, 162.9, 159.6, 159.3, 155.0, 130.5, 130.3, 113.4, 107.7, 97.2, 91.5, 55.6, 55.3, 55.2, 34.0, 25.7, 18.1, -4.2. HRFABMS (m/z) calcd for $C_{23}H_{32}O_5Si$, 417.2097; found 417.2092 (MH^+).

5-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-4-hydroxy-4-(4-methoxyphenyl)-1-pentene (10). To a solution of 4.16 g of **9** (9.99 mmol) in 40 mL of THF was added 20 mL of allylmagnesium bromide (20.0 mmol) in 1 M Et_2O solution at -78 °C. The solution was stirred for 2 h at -78 °C. Then, the reaction mixture was diluted with $CHCl_3$ and washed with 1 *N* HCl and brine successively. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/3) to give 4.39 g (96%) of **10** as a colorless oil . IR (neat) ν_{max} 1608, 1587, 1510, 1464, 1248, 1149, 1109, 835 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (2H, m), 6.85-6.80 (2H, m), 6.10 (1H, d, *J*=2.4 Hz), 6.09 (1H, d, *J*=2.4 Hz), 5.63 (1H, dddd, *J*=17.0, 10.3, 7.3, 6.6 Hz), 4.92 (1H, dd, *J*=17.0, 2.3 Hz), 4.89 (1H, dd, *J*=10.3, 2.3 Hz), 3.79 (3H, s), 3.76 (3H, s), 3.69 (3H, s), 3.18 (1H, d, *J*=14.2 Hz), 2.96 (1H, d, *J*=14.2 Hz), 2.69 (1H, dd, *J*=14.2, 6.6 Hz), 2.43 (1H, dd, *J*=14.2, 7.3 Hz), 1.03 (9H, s), 0.25 (3H, s), 0.24 (3H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.3, 159.2, 147.7, 155.3, 139.8, 135.2, 126.7, 116.8, 112.8, 109.3, 97.5, 91.8, 77.7, 55.4, 55.2, 55.1, 45.3, 37.5, 25.9, 18.3, -3.8, -4.0. HRFABMS (m/z) calcd for $C_{26}H_{39}O_5Si$, 459.2567; found 459.2559 (MH^+).

5-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)-1,2,4-pentanetriol (11). To a solution of 7.11 g of **10** (15.5 mmol) in 140 mL of THF were successively added 5.0 mL of 4% OsO_4 aqueous solution (0.79 mmol) and 2.72 g of NMO (23.2 mmol) at 0 °C. The mixture was stirred for 4 h at rt. Then, H_2O was added to the reaction mixture, and the mixture was extracted three times with EtOAc. Combined organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$=1/10) to give 7.40 g (97%) of **11** as a colorless oil. The product was obtained as a diastereomeric mixture (1:1). IR (neat) ν_{max}

1610, 1585, 1464, 1248, 1149, 1128, 1109 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (2H, m), 6.90-6.80 (2H, m), 6.14 (1H×1/2, d, *J*=2.4 Hz), 6.10 (1H×1/2, d, *J*=2.4 Hz), 6.09 (1H×1/2, d, *J*=2.4 Hz), 6.07 (1H×1/2, d, *J*=2.4 Hz), 3.81 (3H×1/2, s), 3.79 (3H×1/2, s), 3.77 (3H×1/2, s), 3.75 (3H×1/2, s), 3.74 (3H×1/2, s), 3.70 (3H×1/2, s), 3.85-3.65 (1H×1/2, m), 3.55-3.45 (1H×1/2, m), 3.43 (1H×1/2, dd, *J*=11.2, 3.4 Hz), 3.40 (1H×1/2, dd, *J*=11.0, 3.7 Hz), 3.38 (1H×1/2, dd, *J*=11.2, 5.9 Hz), 3.31 (1H×1/2, dd, *J*=11.0, 6.1 Hz), 3.23 (1H×1/2, d, *J*=14.4 Hz), 2.18 (1H×1/2, dd, *J*=14.7, 7.6 Hz), 1.93 (1H×1/2, dd, *J*=14.7, 4.9 Hz), 1.90 (1H×1/2, dd, *J*=14.2, 1.5 Hz), 1.83 (1H×1/2, dd, *J*=14.2, 10.0 Hz), 1.03 (9H, s), 0.29 (3H×1/2, s), 0.28 (3H×1/2, s), 0.25 (3H×1/2, s), 0.24 (3H×1/2, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.4, 159.3, 159.2, 159.1, 158.1, 158.0, 155.2, 155.0, 139.6, 138.5, 126.6, 126.3, 113.2, 113.1, 108.8, 108.6, 97.7, 92.1, 92.0, 80.1, 78.0, 69.6, 69.5, 67.0, 66.9, 55.6, 55.5, 55.2, 55.2, 44.2, 41.9, 38.1, 37.7, 25.9, 18.3, -3.8, -4.0. HRFABMS (m/z) calcd for $C_{26}H_{39}O_6Si$, 475.2516; found 475.2492 $(MH\text{-}H_2O)^+$.

4-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-3-hydroxy-3-(4-methoxyphenyl)-1-butanal (12). To a solution of 7.38 g of **11** (15.0 mmol) in 140 mL of 50% aqueous THF was added 6.41 g of $NaIO_4$ (30.0 mmol) at 0 °C. The solution was stirred for 1 h at rt. Then, the reaction mixture was diluted with EtOAc and washed with brine. The aqueous layer was extracted with EtOAc twice. Combined organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/3) to give 6.60 g (96%) of **12** as a yellow oil. IR (neat) ν_{max} 1720, 1608, 1585, 1509, 1251, 1149, 1130, 1110, 833 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.47 (1H, d, *J*=2.8 Hz), 7.50-7.40 (2H, m), 6.95-6.85 (2H, m), 6.16 (1H, d, *J*=2.0 Hz), 6.11 (1H, d, *J*=2.0 Hz), 3.81 (3H, s), 3.77 (6H, s), 3.23 (1H, d, *J*=14.2 Hz), 2.95 (1H, d, *J*=14.2 Hz), 2.84 (1H, dd, *J*=16.0, 2.8 Hz), 2.61 (1H, dd, *J*=16.0, 2.8 Hz), 1.03 (9H, s), 0.29 (3H, s), 0.25 (3H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 204.2, 159.7, 159.3, 158.3, 155.3, 139.0, 126.4, 113.5, 108.3, 97.7, 92.0, 76.7, 55.6, 55.2, 53.3, 37.9, 25.9, 18.3, -3.8, -4.0. HRFABMS (m/z) calcd for $C_{25}H_{35}O_5Si$, 443.2254; found 443.2246 $(MH\text{-}H_2O)^+$.

(2*Z* and 2*E*)-4-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-butenals (13). To a solution of 2.02 g of **12** (4.39 mmol) in 22 mL of toluene was added 1.85 g of $CuSO_4{\cdot}H_2O$ (8.78 mmol). The suspension was heated for 15 min at 120 °C in sealed tube. The insoluble material of the mixture was removed by passing through celite and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/10) to give 1.41 g (73%) of *Z*-**13** as a colorless oil and 402 mg (21%) of *E*-**13** as a colorless oil. Geometry of the double bond was determined by following procedure. Major isomer of **13** was reduced to give the corresponding isomer of **14**. Then, its primary hydroxyl group was converted to the corresponding 4-nitrobenzoate, and the TBS group was removed. Thus obtained product was recrystallized from EtOAc-*n*-hexane to afford yellow needle. X-Ray crystallographic analysys of the product showed the *Z* geometry in its olefin moiety. Therefore, the double bond of the major isomer of **13** was determined to be *Z* geometry.

Z-**13**: IR (neat) ν_{max} 1668, 1606, 1591, 1510, 1464, 1421, 1252, 1207, 1151, 1109, 839 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.46 (1H, d, *J*=7.8 Hz), 7.35-7.25 (2H, m), 7.00-6.90 (2H, m), 6.13 (1H, d, *J*=2.4 Hz), 6.06 (1H, d, *J*=2.4 Hz), 5.66 (1H, dt, *J*=7.8, 1.8 Hz), 3.85 (3H, s), 3.78 (6H, s), 3.76 (2H, d, *J*=1.8 Hz), 3.74 (6H, s), 0.94 (9H, s), 0.23 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.1, 166.1, 160.2, 159.8, 159.3, 155.2, 131.1, 130.1, 130.0, 126.9, 126.9, 113.6, 108.4, 96.9, 91.4, 55.6, 55.3, 55.2, 33.3, 25.7, 18.2, -4.0, -4.1. HRFABMS (m/z) calcd for $C_{25}H_{35}O_5Si$, 443.2254; found 443.2232 (MH^+).

E-**13**: IR (neat) ν_{max} 1658, 1604, 1512, 1464, 1254, 1201, 1149, 1109, 837 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.29 (1H, d, *J*=7.8 Hz), 7.50-7.45 (2H, m), 6.80-6.75 (2H, m), 6.22 (1H, d, *J*=7.8 Hz), 5.99 (1H, d, *J*=2.4 Hz), 5.97 (1H, d, *J*=2.4 Hz), 3.90-3.75 (2H, m), 3.78 (3H, s), 3.70 (3H, s), 3.62 (3H, s), 1.03 (9H, s), 0.27 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 192.4, 162.0, 160.5, 159.9, 159.4, 154.1, 132.7, 128.5, 126.7, 113.4, 109.9, 97.2, 91.6, 55.3, 55.2, 55.1, 25.9, 24.9, 18.4, -4.0. HRFABMS (m/z) calcd for $C_{25}H_{35}O_5Si$, 443.2254; found 443.2258 (MH^+).

2*Z*-4-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-buten-1-ol (*Z*-14). To a solution of 1.27 g of *Z*-**13** (2.87 mmol) in 30 mL of CH_2Cl_2 was added 3.39 mL of 0.93 M DIBALH solution in *n*-hexane (3.15 mmol) at -78°C. The solution was stirred for 40 min at -78 °C. To the reaction mixture were successively added 0.5 mL of MeOH, saturated ammonium chloride solution. Then, the mixture was extracted three times with $CHCl_3$. Combined organic layer was washed with 1 *N* HCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/3) to give 1.28 g (quantitative) of *Z*-**14** as a colorless oil. IR (neat) ν_{max} 1606, 1589, 1510, 1464, 1423, 1248, 1201, 1151, 1109, 839 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.15-7.10 (2H, m), 6.90-6.85 (2H, m), 6.14 (1H, d, *J*=2.2 Hz), 6.06 (1H, d, *J*=2.2 Hz), 5.97 (1H, tt, *J*=6.8, 1.7 Hz), 3.99 (1H, d, *J*=6.8 Hz), 3.81 (3H, s), 3.78 (3H, s), 3.74 (3H, s), 3.54 (2H, d, *J*=1.7 Hz), 0.97 (9H, s), 0.23 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.5, 159.2, 158.5, 155.2, 142.5, 133.6, 129.2, 123.7, 123.6, 113.3, 110.5, 97.0, 91.5, 60.5, 55.7, 55.2, 31.9, 25.8, 25.7, 18.2, -4.0, -4.1. HRFABMS (m/z) calcd for $C_{25}H_{37}O_5Si$, 445.2410; found 445.2418 (MH^+).

2*E*-4-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-buten-1-ol (*E*-14). To a solution of 1.17 g of *E*-**13** (2.64 mmol) in 20 mL of CH_2Cl_2 was added 3.20 mL of 0.93 M DIBALH solution in *n*-hexane (2.98 mmol) at -78°C. The solution was stirred for 1 h at -78 °C. To the reaction mixture were successively added 0.5 mL of MeOH, saturated ammonium chloride solution. Then, the mixture was extracted three times with $CHCl_3$. Combined organic layer was washed with 1 *N* HCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/3) to give 965 mg (quantitative) of *E*-**14** as a colorless oil. IR (neat) ν_{max} 1606, 1512, 1464, 1421, 1250, 1201, 1149, 1109, 837 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.20 (2H, m), 6.75-6.65 (2H, m), 6.01 (1H, d, *J*=2.4 Hz), 5.96 (1H, d, *J*=2.4 Hz), 5.81 (1H, t, *J*=7.0 Hz), 4.34 (2H, d, *J*=7.0 Hz), 3.78 (2H, s), 3.75 (3H, s), 3.70 (3H, s), 3.67 (3H, s), 1.01 (9H, s), 0.23 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.6, 158.9, 158.4, 154.4, 143.1, 135.4, 127.9, 125.5,

113.0, 111.0, 97.3, 91.9, 59.3, 55.4, 55.1, 55.1, 25.9, 24.7, 18.3, -4.1. HRFABMS (m/z) calcd for $C_{25}H_{37}O_5Si$, 445.2410; found 445.2403 (MH^+).

2*Z*-1-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-4-methoxycarbonyloxy-2-(4-methoxyphenyl)-2-butene (*Z*-15). To a solution of 1.22 g of *Z*-**14** (2.74 mmol) in 5 mL of CH_2Cl_2 were successively added 0.33 mL of pyridine and 306 mg of methyl chloroformate (3.24 mmol) at 0 °C. The solution was stirred for 30 min at 0 °C. Then, the reaction mixture was diluted with $CHCl_3$ and washed with 1 *N* HCl, saturated $NaHCO_3$, and brine. Combined organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/5) to give 1.38 g (quantitative) of *Z*-**15** as a colorless oil. IR (neat) ν_{max} 1747, 1608, 1591, 1512, 1441, 1267, 1248, 1209, 1151, 1111, 837 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20-7.10 (2H, m), 6.90-6.85 (2H, m), 6.13 (1H, d, *J*=2.2 Hz), 6.05 (1H, d, *J*=2.2 Hz), 5.16 (1H, t, *J*=7.2 Hz), 4.49 (2H, d, *J*=7.2 Hz), 3.81 (3H, s), 3.78 (3H, s), 3.73 (3H, s), 3.71 (3H, s), 3.55 (2H, s), 0.97 (9H, s), 0.22 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.5, 159.3, 158.7, 155.7, 145.9, 133.1, 129.2, 118.1, 113.4, 110.1, 97.0, 96.8, 91.6, 91.4, 66.1, 55.6, 55.2, 55.2, 54.5, 32.1, 25.8, 18.2, -4.1, -4.2. HRFABMS (m/z) calcd for $C_{27}H_{38}O_7Si$, 502.2387; found 502.2388 (M^+).

2*E*-1-(6-*tert*-Butyldimethylsilyloxy-2,4-dimethoxyphenyl)-4-methoxycarbonyloxy-2-(4-methoxyphenyl)-2-butene (*E*-15). To a solution of 973 mg of *E*-**14** (2.19 mmol) in 4 mL of CH_2Cl_2 were successively added 0.26 mL of pyridine and 245 mg of methyl chloroformate (2.59 mmol) at 0°C. The solution was stirred for 30 min at 0 °C. Then, the reaction mixture was diluted with $CHCl_3$ and washed with 1 *N* HCl, saturated $NaHCO_3$, and brine. Combined organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/5) to give 1.10 g (quantitative) of *E*-**15** as a colorless oil. IR (neat) ν_{max} 1747, 1608, 1512, 1263, 1203, 1149, 1109, 837 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25-7.20 (2H, m), 6.75-6.65 (2H, m), 5.99 (1H, d, *J*=2.4 Hz), 5.93 (1H, d, *J*=2.4 Hz), 5.66 (1H, t, *J*=6.8 Hz), 4.95 (2H, d, *J*=6.8 Hz), 3.79 (3H, s), 3.79 (1H, d, *J*=12.7 Hz), 3.75 (3H, s), 3.72 (1H, d, *J*=12.7 Hz), 3.70 (3H, s), 3.65 (3H, s), 0.99 (9H, s), 0.22 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.8, 158.9, 158.5, 155.9, 154.3, 144.2, 135.1, 128.0, 127.9, 120.5, 120.5, 112.9, 110.6, 97.0, 91.5, 65.6, 55.3, 55.2, 55.1, 54.6, 25.9, 25.8, 24.9, 18.3, -4.1, -4.1. HRFABMS (m/z) calcd for $C_{27}H_{38}O_7Si$, 502.2387; found 502.2386 (M^+).

2*Z*-1-(2,4-Dimethoxy-6-hydroxyphenyl)-4-methoxycarbonyloxy-2-(4-methoxyphenyl)-2-butene (*Z*-16). To a solution of 202 mg of *Z*-**15** (0.401 mmol) in 0.6 mL of THF was added 0.6 mL of 1 M TBAF solution (0.600 mmol) in THF at 0 °C. The solution was stirred for 15 min at 0 °C. Then, THF was evaporated. The resulting residue was dissolved in EtOAc and wahed with 1 *N* HCl and brine successively. Organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/3) to give 156 mg (quantitative) of *Z*-**16** as a colorless oil. IR (neat) ν_{max} 1747, 1608, 1512, 1267, 1248, 1201, 1147, 1095 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.15-7.10 (2H, m), 6.90-6.80 (2H, m), 6.06 (1H, d, *J*=2.4 Hz), 6.03 (1H, d, *J*=2.4

Hz), 5.47 (1H, tt, *J*=7.2, 1.3 Hz), 4.53 (2H, d, *J*=7.2 Hz), 3.80 (3H, s), 3.74 (3H, s), 3.73 (3H, s), 3.71 (3H, s), 3.63 (2H, d, *J*=1.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.7, 159.1, 158.9, 155.6, 145.6, 131.9, 129.1, 119.4, 119.3, 113.5, 105.5, 93.7, 91.5, 65.9, 55.7, 55.2, 54.7, 31.8. HRFABMS (m/z) calcd for $C_{21}H_{24}O_7$, 388.1522; found 388.1516 (M^+).

2*E*-1-(2,4-Dimethoxy-6-hydroxyphenyl)-4-methoxycarbonyloxy-2-(4-methoxyphenyl)-2-butene (*E*-16). To a solution of 1.10 g of *E*-**15** (2.19 mmol) in 3.3 mL of THF was added 3.3 mL of 1 M TBAF (3.30 mmol) solution in THF at 0 °C. The solution was stirred for 30 min at 0 °C. Then, THF was evaporated. The resulting residue was dissolved in EtOAc and wahed with 1 *N* HCl and brine, successively. Organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/2) to give 722 mg (85%) of *E*-**16** as a colorless oil. IR (neat) ν_{max} 1745, 1610, 1512, 1250, 1201, 1178, 1146 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.20 (2H, m), 6.80-6.70 (2H, m), 5.97 (1H, d, *J*=2.4 Hz), 5.92 (1H, d, *J*=2.4 Hz), 5.74 (1H, t, *J*=7.0 Hz), 4.98 (2H, d, *J*=7.0 Hz), 3.86 (2H, s), 3.81 (3H, s), 3.75 (3H, s), 3.73 (3H, s), 3.67 (3H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.5, 159.0, 158.7, 156.1, 155.8, 144.8, 134.2, 127.9, 121.4, 113.3, 105.6, 93.8, 91.2, 64.9, 55.5, 55.2, 54.9, 24.0. HRFABMS (m/z) calcd for $C_{21}H_{24}O_7$, 388.1522; found 388.1494 (M^+).

4,6-Dimethoxy-2-(4-methoxyphenyl)-2-vinyl-2,3-dihydrobenzofuran (17). From *Z*-**16**: A suspension of 41.7 mg of *Z*-**16** (0.107 mmol) and 12.4 mg of $Pd(PPh_3)_4$ (10.7 μmol) in 1 mL of MeCN was degassed by three repeated FPT method (freezed by liquid nitrogen, evacuation and worming to room temperatrue, and introduction of argon). The reaction mixture was stirred for 2 h at rt. During the reaction, the suspension was turned into amber solution. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/3) to give 33.4 mg (quantitative) of **17** as a colorless oil. From *E*-**16**: A suspension of 710 mg of *E*-**16** (1.83 mmol) and 212 mg of $Pd(PPh_3)_4$ (0.183 mmol) in 19 mL of MeCN was degassed by three repeated FPT method. The reaction mixture was stirred for 26 h at rt. During the reaction, the suspension was turned into amber solution. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/3) to give 537 mg (94%) of **17** as a colorless oil in 94% yield. IR (KBr) ν_{max} 1610, 1504, 1255, 1214, 1146, 1036, 825 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45-7.35 (2H, m), 6.95-6.85 (2H, m), 6.19 (1H, dd, *J*=17.1, 10.7 Hz), 6.18 (1H, d, *J*=2.0 Hz), 6.01 (1H, d, *J*=2.0 Hz), 5.15 (1H, dd, *J*=10.7, 1.3 Hz), 3.78 (3H, s), 3.77 (3H, s), 3.76 (3H, s), 3.43 (1H, d, *J*=14.9 Hz), 3.37 (1H, d, *J*=14.9 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.7, 160.5, 158.8, 156.5, 141.2, 136.0, 126.7, 113.6, 104.9, 91.8, 91.2, 88.4, 55.5, 55.2, 39.8. HRFABMS (m/z) calcd for $C_{19}H_{20}O_4$, 312.1362; found 312.1352 (M^+).

2-(1,2-Dihydroxyethyl)-4,6-dimethoxy-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran (18). To a solution of 537 mg of **17** (1.72 mmol) in 5 mL of THF were successively added 1.25 mL of

4% OsO_4 aqueous solution (0.198 mmol) and 302 mg of NMO (2.58 mmol) at 0 °C. The mixture was stirred for 20 h at rt. Then, H_2O was added to the reaction mixture, and the mixture was extracted three times with EtOAc. Combined organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc only) to give 596 mg (quantitative) of **18** as a colorless foam. The product was obtained as a diastereomeric mixture (3:2). IR (neat) ν_{max} 1612, 1504, 1252, 1217, 1200, 1146, 1107, 1045 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45-7.40 (2H×3/5, m), 7.35-7.28 (2H×2/5, m), 6.93-6.85 (2H, m), 6.17 (1H×2/5, d, *J*=2.4 Hz), 6.13 (1H×3/5, d, *J*=2.0 Hz), 6.00 (1H×2/5, d, *J*=2.0 Hz), 5.99 (1H×3/5, d, *J*=2.0 Hz), 3.98 (1H×3/5, dd, *J*=7.1, 3.2 Hz), 3.95-3.90 (1H×2/5, m), 3.84 (3H×3/5, s), 3.81 (1H×2/5, d, *J*=15.1 Hz), 3.79 (3H×2/5, s), 3.77 (3H×2/5, s), 3.76 (3H×3/5, s), 3.76 (3H×3/5, s), 3.74 (3H×2/5, s), 3.67 (1H×3/5, dd, *J*=11.5, 3.2 Hz), 3.62 (1H×3/5, d, *J*=15.1 Hz), 3.45 (1H×2/5, dd, *J*=11.5, 3.2 Hz), 3.27 (1H×3/5, d, *J*=15.1 Hz), 3.19 (1H×2/5, d, *J*=15.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.6, 161.6, 160.2, 159.9, 159.1, 158.9, 156.6, 134.8, 133.8, 126.9, 126.9, 126.1, 126.0, 113.9, 113.7, 105.3, 105.1, 94.1, 93.3, 91.7, 91.5, 88.4, 88.3, 76.6, 76.5, 55.5, 55.3, 55.3, 37.8, 37.5. HRFABMS (m/z) calcd for $C_{19}H_{23}O_6$, 347.1495; found 347.1496 (MH^+).

4,6-Dimethoxy-2-formyl-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran (19). To a solution of 1.72 g of **18** (4.97 mmol) in 34 mL of 50% aqueous THF was added 2.12 g of $NaIO_4$ (9.91 mmol) at 0 °C. The solution was stirred for 1 h at rt. Then, the reaction mixture was diluted with EtOAc and washed with brine. The aqeous layer was extracted with EtOAc twice. Combined organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/3) to give 1.50 g (96%) of **19** as a colorless oil. IR (neat) ν_{max} 1734, 1612, 1506, 1252, 1219, 1200, 1146 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.61 (1H, s), 7.47-7.37 (2H, m), 6.95-6.90 (2H, m), 6.25 (1H, d, *J*=1.9 Hz), 6.04 (1H, d, *J*=1.9 Hz), 3.92 (1H, d, *J*=15.1 Hz), 3.80 (3H, s), 3.78 (3H, s), 3.77 (3H, s), 3.19 (1H, d, *J*=15.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.4, 161.9, 159.8, 159.7, 156.6, 129.1, 127.0, 126.9, 114.4, 114.3, 104.4, 94.7, 92.1, 88.6, 55.6, 55.4, 55.3, 35.0. HRFABMS (m/z) calcd for $C_{18}H_{19}O_5$, 315.1232; found 315.1244 (MH^+).

4,6-Dimethoxy-2-(α-hydroxybenzyl)-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran (20). To a solution of 1.05 g of **19** (3.34 mmol) in 20 mL of THF was added 3.3 mL of phenylmagnesium bromide (6.60 mmol) in 2 M THF solution at 0 °C. The solution was stirred for 30 min at 0 °C. Then, the reaction mixture was diluted with $CHCl_3$ and washed with saturated ammonium chloride solution and brine successively. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/6) to give 939 mg (72%) of **20** as a white foam. IR (neat) ν_{max} 1612, 1504, 1250, 1217, 1200, 1144, 1109 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25-7.00 (7H, m), 6.80-6.72 (2H, m), 6.19 (1H×3/5, d, *J*=2.0 Hz), 6.16 (1H×2/5, d, *J*=2.0 Hz), 5.99 (1H×3/5, d, *J*=2.0 Hz), 5.97 (1H×2/5, d, *J*=2.0 Hz), 4.97 (1H×2/5, s), 4.93 (1H×3/5, s), 3.77 (3H×3/5, s), 3.76 (3H×2/5, s), 3.75 (1H×2/5, d, *J*=15.1 Hz), 3.75 (3H×3/5, s), 3.75 (3H×2/5, s), 3.75 (3H×3/5, s), 3.74 (3H×2/5, s), 3.71 (1H×3/5, d, *J*=15.1 Hz), 3.24 (1H×3/5, d, *J*=15.1 Hz), 3.13

(1H×2/5, d, *J*=15.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.6, 161.5, 160.2, 160.1, 159.0, 158.8, 156.4, 156.4, 138.5, 138.0, 133.6, 133.5, 128.1, 127.9, 127.8, 127.7, 127.4, 113.0, 112.9, 105.8, 105.5, 95.7, 94.8, 91.4, 91.4, 88.5, 79.5, 79.4, 79.2, 79.1, 55.5, 55.3, 55.2, 36.8, 33.6. HRFABMS (m/z) calcd for $C_{24}H_{25}O_5$, 393.1702; found 393.1703 (MH^+).

4,6-Dimethoxy-2-benzoyl-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran (21). To a solution of 197 mg of **20** (0.501 mol) in 2 mL of CH_2Cl_2 were successively added 8.8 mg of TPAP (25.0 μmol), 88.0 mg of NMO (0.751 mol), and 25.1 g of 4Å MS at 0 °C. The mixture was stirred for 1 h at rt. Then, insoluble materials of the mixture were filtered off through celite and the resulting filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/5) to give 196 mg (quantitative) of **21** as a white foam. IR (KBr) ν_{max} 1682, 1610, 1506, 1254, 1219, 1144 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80-7.95 (2H, m), 7.50-7.40 (3H, m), 7.35-7.30 (2H, m), 6.90-6.85 (1H, m), 6.17 (1H, d, *J*=2.2 Hz), 6.03 (1H, d, *J*=2.2 Hz), 4.34 (1H, d, *J*=15.5 Hz), 3.76 (3H, s), 3.76 (3H, s), 3.75 (3H, s), 3.17 (1H, d, *J*=15.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.4, 161.6, 159.8, 159.2, 156.6, 134.6, 133.8, 132.6, 130.7, 128.0, 125.6, 114.3, 104.5, 96.7, 92.0, 88.5, 55.5, 55.3, 55.2, 39.1. HRFABMS (m/z) calcd for $C_{24}H_{23}O_5$, 391.1545; found 391.1561 (MH^+).

2*E*-3-[4,6-Dimethoxy-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran-2-yl]-3-phenylpropenoic acid ethyl ester (22). To a suspension of 92.2 mg of 60% NaH (2.31 mmol) in 3 mL of THF was added 646 mg of ethyl diethylphosphonoacetate (2.88 mmol) at 0 °C, and the mixture was stirred for 30 min at rt. Then, to the mixture was added a solution of 112 mg of **21** (0.288 mmol) in 3 mL of THF at 0 °C, and the mixture was refluxed for 3 h at 80 °C. The reaction mixture was concentrated *in vacuo*, and the resulting residue was dissolved in EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/5) to give 133 mg (quantitative) of **22** as a white powder: mp 93~94 °C ($CHCl_3$). IR (KBr) ν_{max} 1722, 1628, 1610, 1506, 1221, 1146, 1111, 1038 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28-7.15 (5H, m), 6.85-6.80 (2H, m), 6.70-6.65 (2H, m), 6.49 (1H, s), 6.18 (1H, d, *J*=2.0 Hz), 6.01 (1H, d, *J*=2.0 Hz), 3.89 (2H, q, *J*=7.2 Hz), 3.79 (3H, s), 3.77 (3H, s), 3.76 (3H, s), 3.56 (1H, d, *J*=15.1 Hz), 3.39 (1H, d, *J*=15.5 Hz), 0.97 (3H, t, *J*=7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.1, 161.7, 159.9, 159.2, 159.1, 156.4, 136.5, 133.0, 128.8, 128.1, 127.4, 117.6, 113.3, 104.8, 93.8, 91.6, 88.7, 59.9, 55.5, 55.3, 55.2, 36.5, 13.8. HRFABMS (m/z) calcd for $C_{28}H_{28}O_6$, 460.1886; found 460.1843.1561 (M^+).

3-[4,6-Dimethoxy-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran-2-yl]-3-phenylpropanoic acid ethyl ester (23). To a solution of 46.3 mg of **22** (0.101 mmol) in 1.5 mL of EtOAc was added 11.7 mg of 10% Pd/C. The suspension was stirred for 4 h under argon atmosphere at rt. Then, the catalyst was removed by celite and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/6) to give 46.7 mg (quantitative) of **23** as a colorless oil in yield. The product was obtained as a diastereomeric mixture (7:3). IR (neat) ν_{max} 1728, 1612, 1512,

1254, 1146, 1111, 1041, 829, 810, 702 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-6.95 (7H, m), 6.87-6.82 (2H×7/10, m), 6.17 (1H×3/10, d, *J*=2.0 Hz), 6.16 (1H×7/10, d, *J*=2.0 Hz), 5.99 (1H×3/10, d, *J*=2.0 Hz), 5.85 (1H×7/10, d, *J*=2.0 Hz), 3.88 (1H×3/10, dd, *J*=11.0, 4.2 Hz), 3.83 (1H×3/10, q, *J*=7.1 Hz), 3.82 (1H×7/10, q, *J*=7.1 Hz), 3.78 (3H×3/10, s), 3.77 (3H×7/10, s), 3.76 (3H×7/10, s), 3.75 (3H×3/10, s), 3.73 (3H×3/10, s), 3.67 (3H×7/10, dd, *J*=11.0, 4.2 Hz), 3.61 (3H×7/10, s), 3.58 (1H×3/10, d, *J*=15.5 Hz), 3.28 (1H×7/10, d, *J*=15.5 Hz), 3.22 (1H×3/10, d, *J*=15.5 Hz), 3.10 (1H×7/10, d, *J*=15.5 Hz), 3.02 (1H×3/10, dd, *J*=15.9, 4.2 Hz), 2.87 (1H×7/10, dd, *J*=15.9, 11.0 Hz), 2.66 (1H×7/10, dd, *J*=15.9, 11.0 Hz), 3.75 (3H×2/5, s), 2.61 (1H×3/10, dd, *J*=15.9, 4.2 Hz), 1.01 (1H×3/10, 7, *J*=7.1 Hz), 0.97 (1H×7/10, t, *J*=7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.3, 172.2, 161.7, 161.4, 160.5, 158.6, 158.4, 156.4, 156.2, 139.1, 138.8, 137.2, 135.2, 127.9, 127.6, 127.5, 126.9, 126.7, 113.5, 112.7, 105.2, 105.1, 94.2, 94.2, 91.2, 91.0, 88.4, 88.2, 60.2, 60.1, 55.5, 55.5, 55.3, 55.2, 55.1, 52.1, 39.2, 38.5, 36.5, 35.9, 13.9, 13.9. HRFABMS (m/z) calcd for $C_{28}H_{31}O_6$, 463.2121; found 463.2086 (MH^+).

3-[4,6-Dimethoxy-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran-2-yl]-3-phenylpropanal (24). To a solution of 135 mg of **23** (2.87 mmol) in 3 mL of CH_2Cl_2 was added 0.38 mL of 0.93 M DIBALH solution in *n*-hexane (0.353 mmol) at -78°C. The solution was stirred for 20 min at -78°C. To the reaction mixture were successively added MeOH (1.0 mL), and saturated aqueous ammonium chloride solution. Then, the mixture was extractedthree times with $CHCl_3$. Combined organic layer was washed with 1 *N* HCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/3) to give 112 mg (quantitative) of **24** (0.242 mmol) as a colorless oil. The product was obtained as a diastereomeric mixture (7:3). IR (neat) ν_{max} 1722, 1612, 1504, 1252, 1217, 1146, 1039 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.59 (1H×3/10, d, *J*=1.8 Hz), 9.42 (1H×7/10, d, *J*=1.8 Hz), 7.35-7.30 (2H×7/10, m), 7.30-6.90 (5H, m), 7.03-6.98 (2H×3/10, m), 6.87-6.82 (2H×7/10, m), 6.75-6.70 (2H×3/10, m), 6.17 (1H×3/10, d, *J*=2.0 Hz), 6.17 (1H×7/10, d, *J*=2.0 Hz), 6.02 (1H×3/10, d, *J*=2.0 Hz), 5.87 (1H×7/10, d, *J*=2.0 Hz), 3.85-3.70 (1H, m), 3.78 (3H×3/10, s), 3.77 (3H×7/10, s), 3.76 (3H, s), 3.75 (3H×3/10, s), 3.62 (3H×7/10, s), 3.56 (1H×3/10, d, *J*=14.9 Hz), 3.29 (1H×7/10, d, *J*=14.9 Hz), 3.19 (1H×3/10, d, *J*=14.9 Hz), 3.11 (1H×7/10, d, *J*=14.9 Hz), 3.05 (1H×3/10, ddd, *J*=17.1, 4.8, 1.8 Hz), 3.01 (3H×7/10, ddd, *J*=17.1, 9.3, 1.8 Hz), 2.73 (1H×7/10, dd, *J*=17.1, 4.8, 1.8 Hz), 2.71 (1H×3/10, ddd, *J*=17.3, 9.3, 1.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.4, 201.0, 161.8, 161.5, 160.4, 160.2, 158.7, 156.6, 156.3, 139.2, 128.6, 137.1, 134.3, 130.0, 129.8, 128.2, 128.0, 127.8, 127.2, 127.1, 126.7, 113.6, 112.8, 105.2, 105.1, 94.5, 94.3, 91.5, 91.1, 88.5, 88.3, 60.4, 55.6, 55.5, 55.3, 55.2, 55.2, 55.2, 50.0, 49.8, 45.6, 44.9, 39.0, 38.2, 21.1, 14.2. HRFABMS (m/z) calcd for $C_{26}H_{27}O_5$, 419.1858; found 419.1845 (MH^+).

3*S-3-[2*S**-4,6-Dimethoxy-2-(4-methoxyphenyl)-3-oxo-2,3-dihydrobenzofuran-2-yl]-3-phenylpropanal (3).** To a solution of 53.4 mg of **24** (0.128 mmol) in 1 mL of 1,4-dioxane was added 57.7 mg of DDQ (0.254 mmol) at 0 °C. The solution was stirred for 40 min at rt. Then, the reaction mixture was extracted with EtOAc three times. The organic layer was washed with brine, dried over Na_2SO_4, and

concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/1) to give 30.9 mg (80% based on diastereomeric mixture of the substrate (**24**)) of **3** as a white powder. Another diastereomer of **3** was not obtained. The physicochemical property of thus obtaine **3** was fully identical to that of reported one[3].

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