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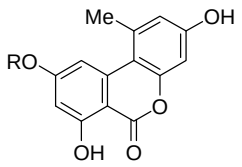
# SYNTHESIS OF ALTERNARIOL THROUGH AN INTRAMOLECULAR BIARYL COUPLING REACTION USING PALLADIUM REAGENT

**Hitoshi Abe,[a]* Tomoko Fukumoto,[b] Yasuo Takeuchi,[b] and Takashi Harayama[c]***

a) Advanced Science Research Center, Okayama University, Okayama 700-8530, Japan, b) Faculty of Pharmaceutical Sciences, Okayama University, Okayama 700-8530, Japan, c) Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, Sanuki-shi, Kagawa 769-2193, Japan
abe@pharm.okayama-u.ac.jp; harayama@kph.bunri-u.ac.jp

**Abstract** – The facile synthesis of alternariol was accomplished through an intramolecular biaryl coupling reaction of the phenyl benzoate derivative, which was prepared by the simple esterification of the corresponding phenol and benzoic acid using a palladium reagent. The regioselectivity during the biaryl coupling reaction was also investigated.

Alternariol (**1**) is the main metabolic product, which is produced by *Alternaria* fungi, and this compound exhibits a significant mycotoxicity and other biological activities.[1] Because of such interesting properties, several attempts for the total synthesis of alternariol (**1**) have been reported.[2] In 2005, Podlech *et al.* demonstrated the short-step synthesis of **1** using the Suzuki-Miyaura coupling reaction as the key step.[3] In their synthesis, however, the final step, which involves a demethylation process, was incomplete so that a small amount of the 9-methyl ether (**2**) contaminated the final product.

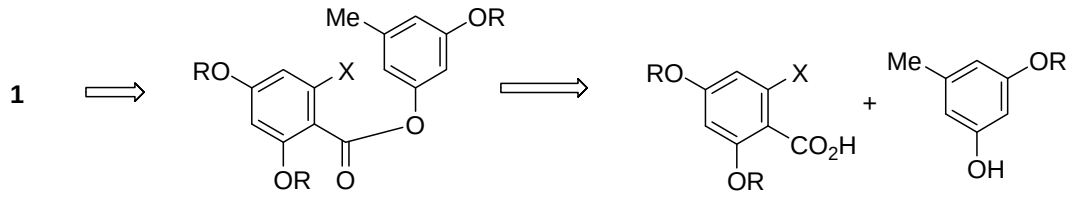



**1**: R = H: alternariol
**2**: R = Me: alternariol 9-methyl ether

In this report, we demonstrate another strategy for the synthesis of alternariol. A palladiun mediated-biaryl coupling reaction of phenyl benzoate derivatives is a well known method for the formation of a dibenzopyran-5-one skeleton.[4] Thus, this technique was expected to be useful for the facile synthesis of **1**. The retro-synthetic outline is summarized in Scheme 1, *i.e.*, phenyl benzoate

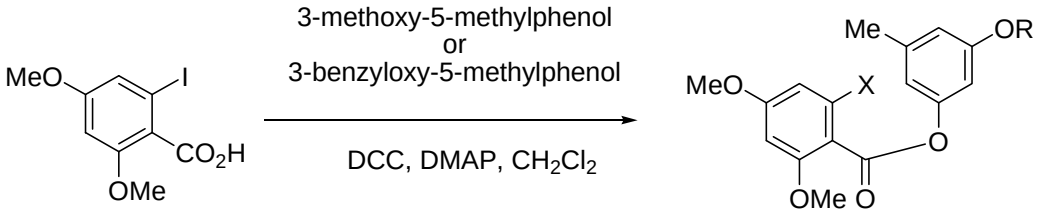
This paper is dedicated to Prof. Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

would be an appropriate precursor of the biaryl coupling reaction, which could be prepared by a simple esterification between the corresponding phenol and benzoic acid.




**Scheme 1** Synthetic outline for alternariol

For the preparation of the phenyl benzoates (**4a** and **4b**), DCC (dicyclohexylcarbodiimide) and DMAP (*N*, *N*-dimethylaminopyridine) combination was effective for the condensation reaction between the benzoic acid (**3**) and 3-methoxy- or 3-benzyloxy-5-methylphenol (Scheme 2).[5]

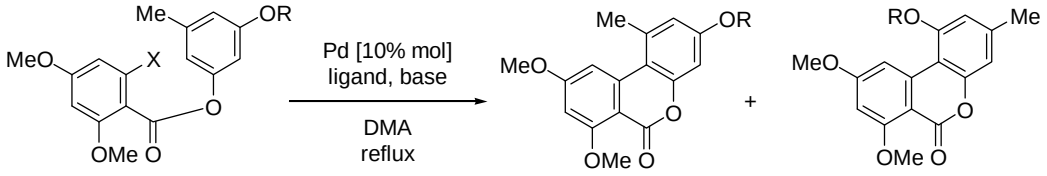



**Scheme 2** Preparation of phenyl benzoates **4a** and **4b**

The palladium-catalyzed reaction of **4a** and **4b** was evaluated under various conditions (Table 1). Initially, we attempted the reaction of **4a** using $Pd(OAc)_2$ (10 mol%), $K_2CO_3$, and P(*o*-tol)$_3$ in DMA (dimethylacetamide) under reflux conditions. The reaction smoothly proceeded to give the lactones (**5a** and **6a**) in good yield while the regioselectivity was quite low (**5a**:**6a** = 1.5:1) (run 1). Changing the ligand produced no significant improvement in the regioselectivity (runs 2-4). When we employed the no-ligand condition, the selectivity was slightly improved (**5a**:**6a** = 1.9:1) (run 5). When $PdCl_2(PPh)_3$ was used as the catalyst, the chemical yield decreased (run 6). Expecting improvement of the regioselectivity by the bulkiness of the alkoxy group, we examined the reaction of the benzyloxy derivative (**4b**). Since the reaction conditions of run 5 showed the most preferable regioselectivity with an acceptable yield, we carried out the reaction of **4b** under similar conditions (run 7). However, it was determined that the alkoxy group on that position did not affect the regioselectivity (run 5 *vs.* run 7).[6]

For completion of the alternariol synthesis, the obtained lactone (**5a**) was treated with $BBr_3$ in $CH_2Cl_2$ to remove the three methyl groups,[7] so that the objective alternariol was obtained (Scheme 3) in a pure form. The spectral data of the synthetic material were identical to the reported ones.

**Table 1** Intramolecular biaryl coupling reaction using palladium reagent



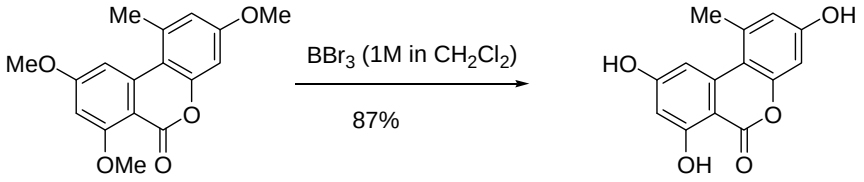

**4a**: R = Me
**4b**: R = Bn

**5a**: R = Me
**5b**: R = Bn

**6a**: R = Me
**6b**: R = Bn

| run | R | Pd | Ligand [L/Pd] *a)* | Base | Time (min) | Yield (%, mixture) | Ratio *b)* **5** : **6** |
|---|---|---|---|---|---|---|---|
| 1 | Me | $Pd(OAc)_2$ | P(*o*-tol)$_3$ [2] | $K_2CO_3$ | 40 | 65 | 1.5 : 1 |
| 2 | Me | $Pd(OAc)_2$ | $PPh_3$ [2] | $K_2CO_3$ | 40 | 71 | 1.0 : 1 |
| 3 | Me | $Pd(OAc)_2$ | $^nBu_3P$ [2] | $K_2CO_3$ | 40 | 71 | 1.1 : 1 |
| 4 | Me | $Pd(OAc)_2$ | DPPP [1], $^nBu_3P$ [1] | $Ag_2CO_3$ | 40 | 73 | 0.6 : 1 |
| 5 | Me | $Pd(OAc)_2$ | —— | $K_2CO_3$ | 40 | 61 | 1.9 : 1 |
| 6 | Me | $PdCl_2(PPh_3)_2$ | —— | NaOAc | 60 | 35 | 1.5 : 1 |
| 7 | Bn | $Pd(OAc)_2$ | —— | $K_2CO_3$ | 40 | 54 | 1.8 : 1 |

*a*) The molar ratio of the ligand and Pd. *b*) Determined by $^1$H-NMR analysis.




**5a**

alternariol (**1**)

**Scheme 3** Removal of three methyl groups for completion of alternariol synthesis

## EXPERIMENTAL

**General:** The melting points were measured using a Yanagimoto micro melting point hot-plate apparatus and are uncorrected. The IR spectra were recorded by a JASCO FTIR-350 spectrophotometer. The NMR spectra were taken using a Varian VXR-500 (500 MHz) or MERCURY (300 MHz) instrument. The chemical shifts are given in δ ppm relative to TMS as the internal standard. The FAB-MS was obtained using a VG Autospec instrument with *m*-nitrobenzyl alcohol as the matrix. An elemental analysis was performed using a Yanaco MT-5 analyzer. Silica gel column chromatography was carried out using Daisogel 1002W (Daiso) or 9385 Kieselgel 60 (Merck). The TLC analysis was performed on Kieselgel 60 $F_{254}$ (Merck) plates.

**2-Iodo-4,6-dimethoxybenzoic acid** (**3**)

To a solution of 3,5-dimethoxyiodobenzene[8] (6.4 g, 24.3 mmol) in dry DMF (20 mL) was added $POCl_3$ (7.9 mL, 84.9 mmol) at 0 °C. The mixture was stirred for 4 h at 90 °C, then poured into ice-water. After the generating precipitates were washed with water, the crude solid of 2-iodo-4,6-dimethoxybenzaldehyde[9] (7.7 g) was obtained. This material was dissolved in a mixture of $CH_3CN$ (70 mL) and $H_2O$ (14 mL), and then 33% $H_2O_2$ (2.43 mL, 26.3 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (4.1 g, 26.3 mmol) were added. After a solution of 80% $NaClO_2$ (3.0 g, 26.3 mmol) in $H_2O$ (14 mL) was added to the mixture, the mixture was stirred for 3 h at rt. A $NaHSO_3$ aqueous solution (5%) was added, and then an extractive work-up with $Et_2O$ and evaporation gave **3** (4.0 g, 54%). Recrystallization from acetone-hexane afforded colorless needles: mp 145-147 °C. IR (KBr) $cm^{-1}$: 3300, 1729, 1700, 1585, 1146, 1111, 1039, 1027, 1012. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 3.82 (3H, s, 4-OMe), 3.85 (3H, s, 6-OMe), 6.46 (1H, d, *J*=2.1 Hz, H-3), 7.00 (1H, d, *J*=2.1 Hz, H-5). *Anal.* Calcd for $C_9H_9O_4$: C, 35.09; H, 2.94. Found: C, 34.97; H, 2.88.

**3-Methyoxy-5-methylphenyl 2-iodo-4,6-dimethoxybenzoate** (**4a**)

DCC (73.8 mg, 0.36 mmol) was added to a solution of **3** (100mg, 0.32 mmol) and 3-methoxy-5-methylphenol (44.9 mg, 0.32 mmol) in $CH_2Cl_2$ (3 mL). The mixture was stirred for 8 h at rt, and then DMAP (11.9 mg, 0.10 mmol) was added. After 16 h, the generated precipitates were collected, dissolved in $CH_2Cl_2$, and washed with $H_2O$, a 10% NaOH aqueous solution, and brine. The $CH_2Cl_2$ layer was dried with anhydrous magnesium sulfate and evaporated to give the crude residue. Purification with silica gel column chromatography (AcOEt : hexane = 1:4) gave **4a** (97.0 mg, 70%): colorless needles, mp 106-108 °C (ether). IR (KBr) $cm^{-1}$: 2875, 1740, 1600, 1250, 1150. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 2.36 (3H, d, *J*=0.6 Hz, Me), 3.81 (3H, s, 3'-OMe), 3.82 (3H, s, 4-OMe), 3.86 (3H, s, 6-OMe), 6.49 (1H, d, *J*=2.1 Hz, H-5), 6.64 (1H, m, H-4'), 6.67 (1H, dd, *J*=2.1 Hz, 2.1 Hz, H-2'), 6.73 (1H, m, H-6'), 6.96 (1H, d, *J*=2.1 Hz, H-3). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 21.7, 55.4, 55.7, 56.1, 92.8, 99.0, 104.7, 112.6, 114.6, 115.2, 122.5, 140.3, 151.5, 158.1, 160.2, 161.8, 165.8. *Anal.* Calcd for $C_{17}H_{17}O_5I$: C, 47.68; H, 4.00. Found: C, 47.84; H, 3.99.

**3-Benzyloxy-5-methylphenyl 2-iodo-4,6-dimethoxybenzoate** (**4b**)

DCC (187.9 mg, 0.91 mmol) was added to a solution of **3** (255.1mg, 0.83 mmol) and 3-benzyloxy-5-methylphenol[10] (177.4 mg, 0.83 mmol) in $CH_2Cl_2$ (5 mL). The mixture was stirred for 17 h at rt, and then DMAP (30.3 mg, 0.25 mmol) was added. After 5 h, the generated precipitates were collected, dissolved in $CH_2Cl_2$, and washed with a cooled 10% aqueous NaOH solution and brine. The $CH_2Cl_2$ layer was dried with anhydrous magnesium sulfate and evaporated to give the crude residue. Purification with silica gel column chromatography (AcOEt : hexane = 1:4) gave **4b** (273.7 mg, 66%) as a colorless oil. IR (neat) $cm^{-1}$: 2950, 1600, 1250, 1160, 1030. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 2.36 (3H, s,

Me), 3.82 (3H, s, 4-OMe), 3.85 (3H, s, 6-OMe), 5.06 (2H, s, Ar-OC*H*$_2$Ph), 6.48 (1H, d, *J*=2.1 Hz, H-5), 6.72 (1H, dd, *J*=1.5 Hz, 0.6 Hz, H-4'), 6.75 (1H, s, H-2'), 6.75 (1H, d, *J*=1.5 Hz, H-6'), 6.96 (1H, d, *J*=2.1 Hz, H-3), 7.33—7.46 (5H, m, C$_6$*H*$_5$). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 21.6, 55.7, 56.1, 70.2, 92.8, 99.0, 105.7, 113.4, 114.9, 115.2, 127.6, 128.0, 128.6, 136.7, 140.3, 151.5, 158.1, 159.4, 161.8, 165.8. MS (FAB, positive ion mode) *m/z*: 505 $[M+1]^+$.

**Typical procedure for the coupling reaction of 4a and 4b** (Table 1)

A mixture of **4a** (100 mg, 0.23 mmol) and $Pd(OAc)_2$ (5.25 mg, 0.02 mmol), $K_2CO_3$ (32.3 mg, 0.23 mmol), P(*o*-tol)$_3$ (14.0 mg, 0.05 mmol), and DMA (3 mL) was heated for 40 min at 190 °C. After cooling, the mixture was diluted with AcOEt and the solid material was filtered off. The filtrate was poured into $H_2O$ and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crude residue. Purification with silica gel column chromatography (AcOEt : hexane = 1:1) gave both **5a** and **6a** in the pure form.

**3,7,9-Trimethoxy-1-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one** (**5a**)

Colorless needles, 155-157 °C ($Et_2O$-$CH_2Cl_2$) [lit.,[1a] 162.5-164 °C]. IR (KBr) $cm^{-1}$: 1710, 1610, 1590, 1360, 1240, 1160. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 2.81 (3H, s, Me), 3.84 (3H, s, 3-OMe), 3.95 (3H, s, 9-OMe), 4.01 (3H, s, 7-OMe), 6.54 (1H, d, *J*=2.1 Hz, H-8), 6.69 (1H, d, *J*=2.7 Hz, H-2 or H-4), 6.72 (1H, d, *J*=2.7 Hz, H-2 or H-4), 7.29 (1H, d, *J*=2.1 Hz, H-10). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 25.6, 55.4, 55.5, 56.3, 97.0, 99.2, 102.3, 103.4, 110.9, 116.2, 137.3, 140.6, 154.0, 158.0, 160.0, 164.0, 164.7. *Anal.* Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.86; H, 5.40. MS (FAB, positive ion mode) *m/z*: 301 $[M+1]^+$.

**1,7,9-Trimethoxy-3-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one** (**6a**)

Colorless needles, 210.5-211.5 °C ($Et_2O$-$CH_2Cl_2$). IR (KBr) $cm^{-1}$: 1725, 1620, 1240, 1220, 1210, 1160, 1150, 1070. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 2.40 (3H, s, Me), 3.40 (3H, s, 1-OMe), 4.00 (3H, s, 9-OMe), 4.01 (3H, s, 7-OMe), 6.55 (1H, d, *J*=2.4 Hz, H-8), 6.62 (1H, d, *J*=1.5 Hz, H-2 or H-4), 6.78 (1H, dd, *J*=1.5 Hz, 0.6 Hz, H-2 or H-4), 8.21 (1H, d, *J*=2.4 Hz, H-10). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 21.7, 55.3, 56.0, 56.3, 97.9, 103.0, 103.2, 105.6, 107.6, 110.3, 139.0, 141.0, 153.0, 156.0, 158.0, 163.5, 165.0. Anal. Calcd for $C_{17}H_{16}O_5 \cdot 1/4\ H_2O$: C, 66.98; H, 5.46. Found: C, 66.80; H, 5.38. MS (FAB, positive ion mode) *m/z*: 301 $[M+1]^+$.

**3-Benzyloxy-7,9-dimethoxy-1-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one** (**5b**)

Colorless needles, 210-212 °C ($CH_2Cl_2$). IR (KBr) $cm^{-1}$: 1730, 1600, 1580, 1560, 1240, 1210, 1160, 1140. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 2.81 (3H, s, Me), 3.95 (3H, s, 9-OMe), 4.01 (3H, s, 7-OMe), 5.10 (2H, s, Ar-OC*H*$_2$Ph), 6.54 (1H, d, *J*=2.1 Hz, H-8), 6.78 (2H, bs, H-2, H-4), 7.31 (1H, d, *J*=2.1 Hz, H-10), 7.34—7.46 (5H, m, C$_6$*H*$_5$). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 25.5, 55.5, 56.3, 70.1, 97.1, 100.3, 102.4,

103.5, 111.1, 116.9, 127.4, 128.2, 128.7, 136.2, 137.3, 140.5, 154.0, 157.9, 159.1, 164.0, 164.7. *Anal.* Calcd for $C_{23}H_{20}O_5$ · 1/4 $H_2O$: C, 72.52; H, 5.43. Found: C, 72.77; H, 5.45. MS (FAB, positive ion mode) *m/z*: 377 $[M+1]^+$.

**1-Benzyloxy-7,9-dimethoxy-3-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one** (**6b**)

Colorless needles, 246-248 °C ($CH_2Cl_2$). IR (KBr) $cm^{-1}$: 1720, 1620, 1600, 1580, 1560, 1460, 1250, 1240, 1210, 1160, 1100, 1070. $^1$H-NMR (300 MHz, $CDCl_3$) δ: 2.42 (3H, s, Me), 3.21 (3H, s, 9-OMe), 3.94 (3H, s, 7-OMe), 5.15 (2H, s, Ar-OC*H*$_2$Ph), 6.46 (1H, d, *J*=2.4 Hz, H-8), 6.75 (1H, d, *J*=1.5 Hz, H-2 or H-4), 6.82 (1H, dd, *J*=1.5 Hz, 0.9 Hz, H-2 or H-4), 7.39—7.56 (5H, m, C$_6$*H*$_5$), 8.07 (1H, d, *J*=2.4 Hz, H-10). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ: 21.8, 54.8, 56.3, 71.6, 99.2, 101.8, 103.3, 105.7, 108.2, 110.6, 128.8, 128.8, 135.8, 139.2, 141.1, 153.1, 157.3, 158.0, 163.2, 165.0. *Anal.* Calcd for $C_{23}H_{20}O_5$ · 1/4 $H_2O$: C, 72.52; H, 5.43. Found: C, 72.25; H, 5.51. MS (FAB, positive ion mode) *m/z*: 377 $[M+1]^+$.

**Alternariol** (**1**)

$BBr_3$ (1 mol/L in $CH_2Cl_2$)[11] (3.9 mL, 3.9 mmol) was added to **4a** (59 mg, 0.20 mmol), and the mixture was stirred for 9h at rt. The mixture was slowly poured into MeOH while cooling. The volatile materials were removed under reduced pressure to give the crude solid. Purification with silica gel column chromatography (MeOH : $CH_2Cl_2$ = 1:50 to 1:10) gave **1** (44.0 mg, 87%) as colorless needles, mp 320-325 °C (decomp.) [lit.[1a] 350 °C (decomp.)]. IR (KBr) $cm^{-1}$: 3445, 3190, 2975, 2560, 2380, 2370, 1660, 1615, 1580, 1515, 1460, 1354, 1290, 1263, 1250, 1200, 1160, 1127, 1107, 1056, 1030, 992, 965, 935, 850, 796, 748, 710, 660. $^1$H-NMR (300 MHz, $CD_3OD$) δ: 2.73 (3H, s, Me), 6.34 (1H, d, *J*=2.0 Hz, H-8), 6.58 (1H, d, *J*=2.6 Hz, H-2 or H-4), 6.67 (1H, d, *J*=2.6 Hz, H-2 or H-4), 7.23 (1H, d, *J*=2.0 Hz, H-10). $^{13}$C-NMR (150 MHz, $CD_3OD$) δ: 25.8 (Me), 99.1(Ar-*C*), 102.0 (Ar-*C*-H), 102.8 (Ar-*C*-H), 105.5 (Ar-*C*-H), 110.9 (Ar-*C*), 118.6 (Ar-*C*-H), 139.8 (Ar-*C*), 140.1 (Ar-*C*), 154.5 (Ar-*C*), 159.9, 166.2, 166.9, 166.9 (4×Ar-*C*-OH, CO). MS (FAB, positive ion mode) *m/z*: 259 $[M+1]^+$. HRMS (FAB) calcd for $C_{14}H_{11}O_5^+$: 259.0606, found 259.0607.

## ACKNOWLEDGEMENTS

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5. 3-Methoxy-5-methylphenol is commercially available, while 3-benzyloxy-5-methylphenol was prepared by the reported method.[10]
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11. Concentration of the reagent was crucial. When a lower concentration of $BBr_3$ was employed, only the partially demethylated products were detected.