*Unselectivity as an Advantage*

# Unselective Phenolic Coupling of Methyl 2-Hydroxy-4-methoxy-6-methylbenzoate—A Valuable Tool for the Total Synthesis of Natural Product Families**

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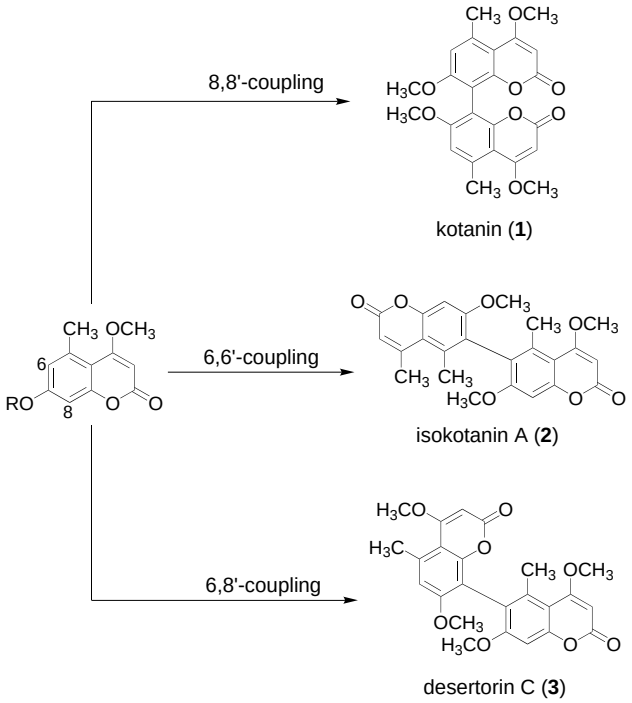
The biaryl axis is a common feature of many herbal, fungal, and bacterial natural products.[1] For many of these biaryl compounds the biosynthesis contains an oxidative phenolic coupling step with a regio- and stereochemistry characteristic of the biological origin.[2] For this reason, families of closely related dimeric phenolic secondary metabolites are found in nature differing only in the linkage and spatial arrangement of their monomeric precursors. This kind of biodiversity is, for example, common to the naphthylisoquinoline alkaloids dioncophylline A, B, and C from *Triphyophyllum peltatum*,[3] to the dimeric dihydroanthracenones flavomannin (*Penicillium wortmannii, Cortinarius odoratus*), atrovirin (*Cortinarius atrovirens*), and phlegmacin (*Cortinarius sp., Cassia torosa*),[4] as well as to the dimeric coumarins kotanin (**1**) (*Aspergillus clavatus*), isokotanin A (**2**) (*Aspergillus alliaceus*), and desertorin C (**3**) (*Emericella desertorum*) (Scheme 1).[5]




***Scheme 1.*** Putative biosynthesis of dimeric coumarins.

In general, biaryl skeletons can be constructed by 1) the classical Ullmann reaction and other reductive processes[6] or 2) the oxidative (biomimetic) phenolic coupling reaction using heavy metal oxidants like thallium(III), vanadium(V), ruthenium(IV), and iron(III) salts.[7] Here we report on a new and highly efficient synthesis of the dimeric coumarins **1**–**3** by an unselective oxidative phenolic coupling reaction of a monomeric orsellinic acid derivative as the key step.

The synthesis of symmetric dimeric orsellinates starting from methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**4**)[8] is well established. Ullmann reaction of the regioselectively iodinated and fully methylated derivatives of **4** followed by regioselective demethylation provided the 3,3′- and 5,5′-dimers **5** and **6**, respectively (see Scheme 2).[9] However, this multistep synthesis is limited to the methyl residue as the protecting group because the Ullmann reaction is sensitive to sterically more demanding substituents.[6] Moreover, the unsymmetrical 3,5′-dimer **7** is not accessible using this strategy.[10] Therefore, a more straightforward and flexible access to dimeric orsellinates would be desirable. In 1997, Harada et al. reported a highly selective oxidative phenolic coupling of 2,4-di-*O*-methylphloroacetophenone (phloroacetophenone = 2,4,6-trihydroxyacetophenone) in the solid state.[11] They heated a mixture of the substrate and iron(III) chloride adsorbed on silica gel at 45 °C for six days and obtained the symmetrical 5,5′-dimer in 81 % yield.

Because of its structural similarity to 2,4-di-*O*-methylphloroacetophenone, methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**4**) seemed to be an appropriate substrate to extend this method to the phenolic coupling of orsellinates. The phenolic coupling was carried out by heating a mixture of **4** and ferric chloride adsorbed on silica gel at 60 °C for 20 h. Remarkably, this reaction required much shorter reaction times and was unselective with regard to the coupling position. After separation by a single flash chromatography on silica gel, the 3,3′-, 5,5′-, and 3,5′-dimers **5**–**7** were obtained in 17, 33, and 30 % yield, respectively (Scheme 2). This reaction was also performed on a 2 g scale with a total yield of 70 %. We assume that the modified reaction behavior (unselectivity and shorter reaction times) results from the electronic differences between 2,4-dimethylphloroacetophenone and **4**. Unselective oxidative phenolic couplings have been known for a long time,[12] however, only one attempt has been made to utilize this unselectivity in diversity-oriented natural product synthesis.[11c]

Starting from the three regioisomeric dimers of orsellinate **4** we designed the synthesis of **1**–**3**. The coumarin core was obtained by a new strategy—the nucleophilic addition of the acetonitrile anion to the carboxy carbon atoms of the dimeric

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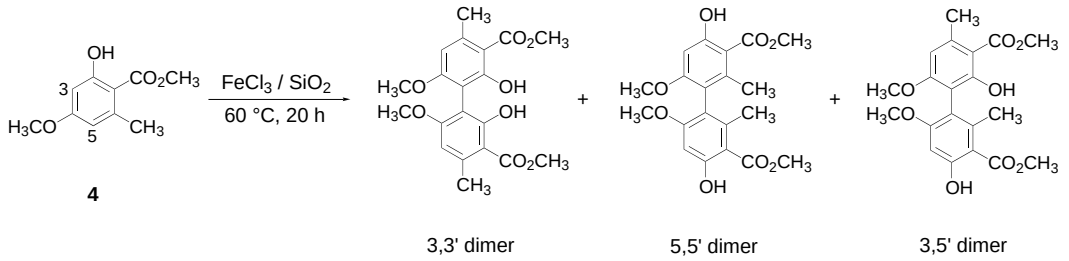
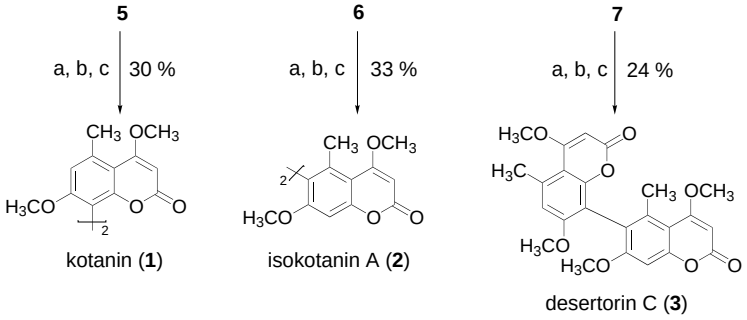
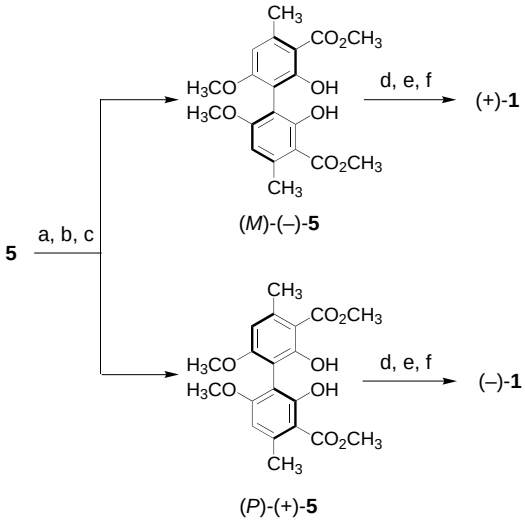



***Scheme 2.*** Oxidative phenolic coupling of monomeric orsellinate **4**.

orsellinates.[13] After acidic hydrolysis followed by methylation of the free hydroxy groups with dimethylsulfate the dimeric coumarins were obtained in 30% yield for kotanin (**1**), 33% yield for isokotanin A (**2**), and 24% yield for desertorin C (**3**; Scheme 3).




***Scheme 3.*** a) MeCN, *n*BuLi, −78 °C to RT; b) HCl, methanol, △; c) NaH, $Me_2SO_4$, HMPT (hexamethylphosphoric triamide).




***Scheme 4.*** a) (−)-camphanic acid chloride, DMAP (4-dimethylaminopyridine), pyridine, 84%; b) chromatographic separation on silica gel (isohexane/ethyl acetate, 1:1); c) NaOMe, methanol, 75%; d) MeCN, *n*BuLi, −78 °C to RT, 75%; e) HCl, methanol, △, 67%; f) NaH, $Me_2SO_4$, HMPT, 59%.

As an example, the atropisomers of the racemic 3,3′-coupled orsellinate **5** were resolved as diastereomeric bis(camphanate) esters obtained with (−)-camphanic acid chloride as the chiral derivatizing agent.[11e] This reaction occurred with a yield of 84%, and the two diastereomers were formed in a ratio of 1:1. After separation ($SiO_2$), the absolute configuration of the biphenyl moiety of the first-eluting diastereomer was determined as *M* by X-ray structure analysis using the known absolute configuration of the camphanate ester residue.[14] Cleavage of the chiral moiety worked with sodium methanolate to give the atropisomeric 3,3′-coupled biaryls (*M*)-(−)-**5** and (*P*)-(+)-**5** in 75% yield. These two enantiomerically pure dimeric orellinates were used in the synthesis of (+)- and (−)-kotanin following the procedure described above (Scheme 4). Since the atropisomers of the two other dimeric orsellinates, **6** and **7**, should also be accessible by enantiomeric resolution or separation by HPLC on a chiral phase the synthesis of both enantiomers of isokotanin A (**2**) and desertorin C (**3**) seems possible.

In summary, a short and very efficient synthesis of the dimeric coumarins kotanin (**1**), isokotanin A (**2**), and desertorin C (**3**) has been presented. As a result of the unselective oxidative phenolic coupling of the monomeric orsellinate **4** all three regioisomeric biaryls are available starting from the same substrate. Thus the procedure mimics the biosynthesis of these natural products. Since the dimeric orsellinates are readily available and highly functionalized other classes of natural products should be similarly accessible.

## *Experimental Section*

Phenolic coupling of **4**: Silica gel (7.24 g) was added to a solution of $FeCl_3 \cdot 6H_2O$ (3.52 g, 13.02 mmol) in diethyl ether (190 mL) and methanol (10 mL). The solvents were removed to give a yellow solid, which was dried at 50 °C in vacuo (0.4 mbar) for 8 h to leave a yellow-green solid. This solid (1.40 g) was given to a solution of **4** (146 mg, 0.74 mmol) in dichloromethane (30 mL). After mixing well, the solvent was removed under reduced pressure to give a dark solid, which was heated at 60 °C for 20 h. Methanol (50 mL) was added, and the mixture was filtered (celite). The solvent was removed in vacuo, and the dark residue was purified by column chromatography (gradient isohexane/ethyl acetate 5:1→2:1) to yield the biphenyldiols

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**5** (22 mg, 17%), **6** (42 mg, 33%), and **7** (38 mg, 30%) as colorless solids.[15]

**5:** $R_f = 0.22$ (isohexane/ethyl acetate, 2:1); M.p. 246°C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 11.81$ (s, 2H, 2 × OH), 6.41 (s, 2H, 2 × Ar-H), 3.91 (s, 6H, 2 × $OCH_3$), 3.77 (s, 6H, 2 × $OCH_3$), 2.59 ppm (s, 6H, 2 × $CH_3$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta = 172.37$ (2 × C=O), 161.90 (2 × $C_q$), 161.50 (2 × $C_q$), 143.10 (2 × $C_q$), 107.84 (2 × $C_q$), 106.69 (2 × CH), 105.97 (2 × $C_q$), 55.82 (2 × $OCH_3$), 51.85 (2 × $OCH_3$), 24.96 ppm (2 × $CH_3$); MS: *m/z* (%): 390 (67) [$M^+$], 358 (70) [$C_{19}H_{18}O_7^+$], 327 (65) [$C_{18}H_{15}O_6^+$], 295 (100) [$C_{17}H_{11}O_5^+$]; HRMS: calcd for $C_{20}H_{22}O_8$ 390.1315; found 390.1311.

**6:** $R_f = 0.33$ (isohexane/ethyl acetate, 2:1); M.p. 183°C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 11.77$ (s, 2H, 2 × OH), 6.41 (s, 2H, 2 × Ar-H), 3.91 (s, 6H, 2 × $OCH_3$), 3.67 (s, 6H, 2 × $OCH_3$), 2.10 ppm (s, 6H, 2 × $CH_3$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta = 172.49$ (2 × C=O), 164.47 (2 × $C_q$), 162.25 (2 × $C_q$), 141.41 (2 × $C_q$), 119.15 (2 × $C_q$), 105.55 (2 × $C_q$), 97.29 (2 × CH), 55.69 (2 × $OCH_3$), 51.83 (2 × $OCH_3$), 19.36 ppm (2 × $CH_3$); MS: *m/z* (%): 390 (47) [$M^+$], 358 (31) [$C_{19}H_{18}O_7^+$], 327 (100) [$C_{18}H_{15}O_6^+$], 295 (100) [$C_{17}H_{11}O_5^+$]; HRMS: calcd for $C_{20}H_{22}O_8$ 390.1315; found 390.1314.

**7:** $R_f = 0.24$ (isohexane/ethyl acetate, 2:1); M.p. 190°C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 11.79$ (s, 1H, OH), 11.74 (s, 1H, OH), 6.44 (s, 1H, Ar-H), 6.38 (s, 1H, Ar-H), 3.92 (s, 3H, $OCH_3$), 3.90 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 3.70 (s, 3H, $OCH_3$), 2.60 (s, 3H, $CH_3$), 2.22 ppm (s, 3H, $CH_3$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta = 172.53$ (C=O), 172.41 (C=O), 164.74 ($C_q$), 162.34 ($C_q$), 161.90 ($C_q$), 161.35 ($C_q$), 142.80 ($C_q$), 141.64 ($C_q$), 115.71 ($C_q$), 111.16 ($C_q$), 106.45 (CH), 105.87 ($C_q$), 105.65 ($C_q$), 97.50 (CH), 55.81 ($OCH_3$), 55.69 ($OCH_3$), 51.91 ($OCH_3$), 51.78 ($OCH_3$), 24.94 ($CH_3$), 19.67 ppm ($CH_3$); MS: *m/z* (%): 390 (53) [$M^+$], 358 (66) [$C_{19}H_{18}O_7^+$], 326 (100) [$C_{18}H_{14}O_6^+$]; HRMS: calcd for $C_{20}H_{22}O_8$ 390.1315; found 390.1323.

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[14] X-ray structure analysis of dimethyl (*M*)-(−)-2,2′-bis(camphanate)-6,6′-dimethoxy-4,4′-dimethyl-1,1′-biphenyldicarboxylate ($C_{40}H_{46}O_{14}$): colorless crystals, crystal dimension 0.30 × 0.35 × 0.40 mm$^3$; $M = 750.77$; monoclinic, space group $P2_1$ (no. 4), $a = 10.5732(2)$, $b = 16.5829(3)$, $c = 11.0339(2)$ Å, $\beta = 105.317(1)°$, $V = 1865.90(6)$ nm$^3$, $Z = 2$, $\mu(Mo_{K\alpha}) = 0.101$ mm$^{-1}$, $T = 123(2)$ K, $F(000) = 796$. 20007 reflections up to $2\theta_{max} = 50.7°$ were measured on a Nonius Kappa-CCD diffractometer with $Mo_{K\alpha}$ radiation, 6614 of which were independent and used for all calculations ($R_{int} = 0.035$). The structure was solved by direct methods and refined to $F^2$ anisotropically, the H atoms were refined with a riding model. The final quality coefficient $wR2(F^2)$ was 0.113, with a conventional $R(F) = 0.043$ for 483 parameters and 165 restraints. One carboxylate group is disordered. The absolute structure cannot be determined reliably (Flack's *x* parameter 0.2(8)). CCDC-197800 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[15] From fractions containing **5** and **7**, the symmetric compound crystallizes quantitatively to give after separation by centrifugation analytically pure (NMR) **5** and **7**.