An Efficient Synthesis of Dihydroxyfluorenones via in Situ Pd(0)-Catalyzed Cross-Coupling

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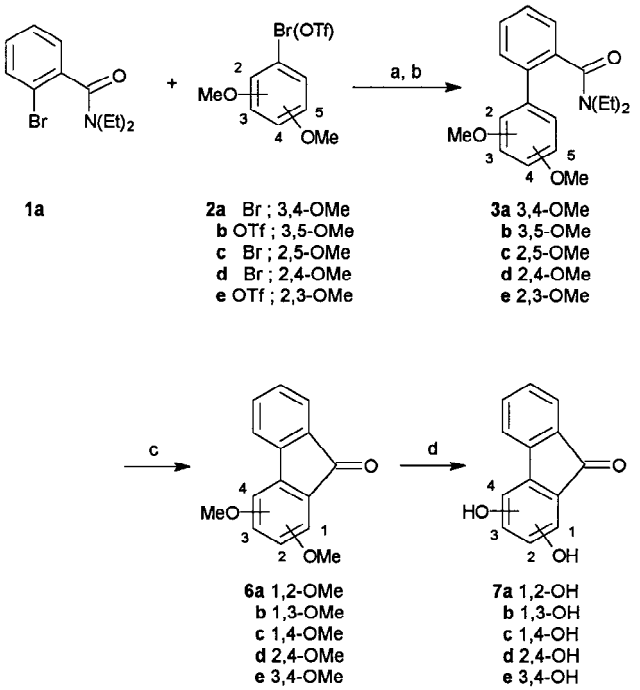
Abstract: All six dimethoxyfluorenones **6a–f** and dihydroxyfluorenones **7a–f**, wherein substitution occurs at only one aromatic ring, were conveniently prepared by palladium(0)-catalyzed cross-coupling reactions of aryl bromides/triflates **2a–e** with in situ generated arylboranes, derived from *o*-bromobenzamide **1a** and *o*-bromophenyloxazoline **1b**.

Key words: dimethoxyfluorenone, dihydroxyfluorenone, in situ Pd(0) cross-coupling, regioselectivity, regioisomers

Fluorenone derivatives are known to display a variety of biological activities.[1–3] Also, several methoxy and hydroxyfluorenone derivatives are natural products whose syntheses have recently been described.[4–9] As part of our investigation into the protein kinase inhibitory activity of substituted fluorenones,[10] we desired a convenient method for preparing all possible dihydroxy regioisomers in which substitution occurs on only one aromatic ring of the fluorenone nucleus.

Some syntheses of fluorenones employ fluorene,[11] benzophenone,[12] or hexahydrofluorenone[13a] precursors. Unfortunately, these procedures either give isomeric mixtures, are low yielding or offer limited access to certain isomers. Increased accessibility of substituted biphenyls through numerous cross-coupling techniques makes the intramolecular acylation reactions of biphenyl carboxylic acids[11] and biphenyl amides[14] an attractive approach to fluorenones. Of note are the recently reported in situ Suzuki cross-coupling methods which obviate the need for isolation of boronic acid intermediates.[15] Furthermore, the respective cyclization chemistries of biaryl-2-carboxylic acids and biaryl-2-carboxamides, the classical and anionic equivalent of the Friedel–Crafts reaction, are complementary and enable the preparation of a complete isomeric set. In an effort to obtain all possible dihydroxyfluorenone regioisomers **7a–f**, we have employed and here report a convenient synthetic approach utilizing, 1) an efficient in situ generation and Pd(0)-catalyzed cross-coupling of aryl boranes to prepare substituted biaryls; 2) regiospecific remote aromatic metalation cyclization; and 3) a complementary Friedel–Crafts acylation cyclization.

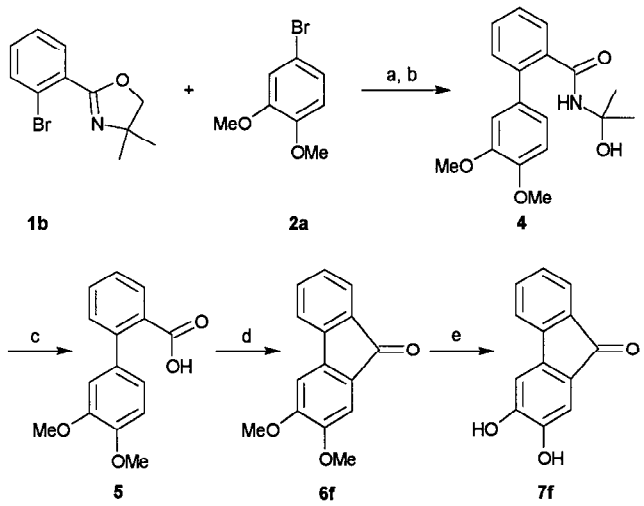
Thus, 2-bromo-*N*,*N*-diethylbenzamide **(1a)** (Scheme 1) undergoes lithium-halogen exchange and boronation at the 2-position. Treatment of the boronate with dimethoxyaryl bromides and aryl triflates **2a–e** under modified in situ Suzuki conditions gave the biarylamides **3a–e**. Intramolecular cyclization occurs when **3a–e** react with LDA in a remote metalation process as described by Snieckus.[14] The five dimethoxyfluorenone regioisomers **6a–e** thus formed are easily demethylated with refluxing HBr/AcOH to give dihydroxyfluorenones **7a–e** in good yield.



Reagents and conditions: a) BuLi/THF, –70 °C, then $B(OMe)_3$, –70 to 0 °C, 1.5 h; b) 2 M Na_2CO_3/ $(PPh_3)_4Pd$/**2a–e**/DME/EtOH, reflux, 16 h (48–82%); c) LDA (2.5 equiv)/THF, –20 °C to r.t., 16 h (76–91%); d) HBr/AcOH, reflux, 16 h (62–92%)

Scheme 1

In order to obtain the sixth regioisomer **7f**, we employed the same in situ coupling procedure using **2a** and oxazoline **1b** as a masked carboxylic acid (Scheme 2). Acid hydrolysis of the ring-opened[16] intermediate **4** gave biaryl-2-benzoic acid **5** which underwent normal Friedel–Crafts cyclization to regioselectively provide 2,3-dimethoxyfluoren-9-one **(6f)** in high yield.[17] Fluorenone **6f** cannot be prepared by the anionic equivalent route since the more acidic of two remote hydrogens is ortho to the methoxy substituent (e.g. **3a** regiospecifically gave **6a**). Demethylation of **6f** provides **7f** in high yield and completes the series of dihydroxyfluorenone regioisomers. Since the viability of using substituted diethyl benzamides[14] and phenyloxazolines[18] has been previously demonstrated, the utility of this combined classical carbonium ion and carbanion mediated approach is further significant considering that regiospecific control is possible on the other half of the molecule (positions five through eight), thereby potentially providing fluorenones of even greater structural diversity.



Reagents and conditions: a) BuLi/THF, –70 °C, then $B(OMe)_3$, –70 to 0 °C, 1.5 h; b) 2 M Na_2CO_3/$(PPh_3)_4Pd$/**2a**/DME/EtOH, reflux, 16 h (57%); c) 4.5 N HCl, 16 h, (70%); d) TFAA/$CHCl_3$ (94%); e) HBr/AcOH, reflux, 16 h (90%)

Scheme 2

In summary, biaryl precursors to methoxyfluorenones **6a–f** were made using a modified in situ Pd(0)-catalyzed cross-coupling method. Dihydroxyfluorenone regioisomers **7a–f** were easily obtained in 30–69% overall yields.

Melting points are uncorrected. ^{1}H NMR spectra were obtained at 300 MHz unless otherwise indicated. All reagents were of commercial quality and all reactions were carried out under an inert atmosphere. 2-Bromo-*N*,*N*-diethylbenzamide **(1a)** and 2-(2-bromophenyl)-4,4-dimethyloxazoline **(1b)** were prepared according to literature procedures.[19a,b]

3,5-Dimethoxyphenyl Trifluoromethanesulfonate (2b); Typical Procedure:

To a solution of 3,5-dimethoxyphenol (10.0 g, 64.9 mmol) in CH_2Cl_2 (500 mL) at 0°C was added Et_3N (25mL). Trifluoromethanesulfonic anhydride (45.0 g, 160 mmol) was added dropwise with stirring. After 30 min, the mixture was allowed to reach r.t. and then poured into aq $NaHCO_3$ solution. The organic layer was seperated, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The brown oil obtained was purified by chromatography on silica gel (30% EtOAc in hexane) and distilled using a Kugelrohr distillation apparatus to give **2b**, identical in all respects to that reported in the literature;[20] yield: 17.5 g (94%); yellow oil; bp 90–95°C / 0.1 Torr.

Using the above procedure (without Kugelrohr distillation), the following compound was prepared:

2,3-Dimethoxyphenyl Trifluoromethanesulfonate **(2e)**: 2,3-Dimethoxyphenol (5.00 g, 32.4 mmol), CH_2Cl_2 (200 mL), Et_3N (12 mL), trifluoromethanesulfonic anhydride (22.0 g, 78.0 mmol); yield: 72%; pale yellow oil.

IR (neat): ν = 1424, 1252, 1215, 1142 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.89 (s, 3 H), 3.95 (s, 3 H), 6.83 (dd, 1 H, *J* = 1.5, 8.4 Hz), 6.92 (dd,1 H, *J* = 1.5, 8.5 Hz), 7.05 (dd, 3 H, *J* = 8.4, 8.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 56.20, 61.26, 112.28, 113.95, 117.12, 120.30, 123.56, 141.58, 142.84, 154.04.

MS (EI, 70eV): *m/z* (%) = 286 (M^+, 71), 153 (100), 125 (62).

***N*,*N*-Diethyl-3′,4′-dimethoxy-2-biphenylcarboxamide (3a); Typical Procedure:**

To a solution of 2-bromo-*N*,*N*-diethylbenzamide (**1a**; 2.90 g, 11.3 mmol) in anhyd THF (50 mL) at –78°C was added BuLi (5 mL, 2.5 M in hexanes). After stirring for 30 min, $B(OMe)_3$ (1.5 g, 14.7 mmol) was added and the mixture warmed to 0°C and stirred 1.5 h. The solvent was evaporated under reduced pressure at r.t., then DME (50 mL), EtOH (2 mL), 2 M aq Na_2CO_3 solution (11.3 mL), $(PPh_3)_4Pd$ (4 mol%, 390 mg) and 4-bromoveratrole (**2a**; 3.2 g, 14.7 mmol) were added. The mixture was heated at reflux for 16 h, then cooled to r.t. and EtOAc (50 mL) added. After washing with brine, the organic layer was seperated, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude material was purified by chromatography on silica gel (40% EtOAc in hexane) to give **3a** (2.0 g, 6.4 mmol); yield: 57%; yellow oil. [LiCl (0.5 g) was also added during the Pd coupling step of triflates **2b** and **2e** to obtain **3b** and **3e]**.

HRMS (FAB, M^+H): calc. 314.175619; found 314.174460.

IR ($CHCl_3$): ν = 1624, 1520, 1252 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.74 (t, 3 H, *J* = 7.3 Hz), 0.95 (t, 3 H, *J* = 7.2 Hz), 2.69 (m, 1 H), 2.95 (m, 1 H), 3.12 (m, 1 H), 3.66 (m, 1 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 6.88 (d, 1 H, *J* = 8.2 Hz), 7.02 (dd, 1 H, *J* = 2.2, 8.2 Hz), 7.10 (d, 1 H, *J* = 2.2 Hz), 7.34–7.43 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 12.26, 13.45, 38.40, 42.31, 55.91, 77.21, 110.96, 112.28, 121.03, 127.00, 127.22, 128.85, 129.24, 132.74, 136.32, 138.09, 148.55, 170.75.

Using the above procedure, the following compounds were prepared:

N,N-Diethyl-3′,5′-dimethoxy-2-biphenylcarboxamide **(3b)**: from **1a** (2.00 g, 7.80 mmol) and **2b** (4.20 g, 14.7 mmol); yield: 82%; pale yellow oil.

IR (neat): ν = 1626, 1595, 1458, 1429, 1155 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 0.74 (t, 3 H, *J* = 7.2 Hz), 0.87 (t, 3 H, *J* = 7.3 Hz), 2.75 (m, 1 H), 2.90 (m, 1 H), 3.02 (m, 1 H), 3.57 (m, 1 H), 3.75 (s, 6 H), 6.50 (t, 1 H, *J* = 2.3 Hz), 6.57 (d, 2 H, *J* = 2.3 Hz), 7.29 (d, 1 H, *J* = 7.2 Hz), 7.39–7.51 (m, 3 H).

^{13}C NMR (DMSO-d_6): δ = 11.88, 13.35, 37.71, 41.90, 55.16, 99.34, 106.62, 126.67, 127.59, 128.81, 129.09, 136.25, 137.52, 141.32, 160.22, 169.21.

MS (EI, 70 eV): *m/z* (%) = 313 (M^+, 76), 241 (100), 214 (96).

N,N-Diethyl-2′,5′-dimethoxy-2-biphenylcarboxamide **(3c)**: from **1a** (2.90 g, 11.3 mmol) and **2c** (3.20 g, 14.7 mmol); yield: 57%; pale yellow oil.

HRMS (FAB, M^+H): *m/z* calc. 314.175619; found 314.175792.

IR (neat): ν = 1628, 1506, 1466, 1221 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 0.73 (t, 3 H, *J* = 7.3Hz), 0.82 (t, 3 H, *J* = 7.3 Hz), 2.70–3.13 (m, 3 H), 3.54 (m, 1 H), 3.64 (s, 3 H), 3.68 (s, 3 H), 6.72 (d, 1 H, *J* = 3.4 Hz), 6.88 (dd, 1 H, *J* = 3.4, 9.1 Hz), 6.98 (d, 1, *J* = 9.1 Hz), 7.28–7.43 (m, 4 H).

^{13}C NMR (DMSO-d_6): δ = 11.73, 13.51, 37.39, 41.58, 55.28, 55.75, 112.09, 113.51, 116.67, 126.07, 127.10, 127.83, 128.70, 130.75, 134.74, 137.12, 150.18, 152.51, 168.95.

N,N-Diethyl-2′,4′-dimethoxy-2-biphenylcarboxamide **(3d)**: from **1a** (2.90 g, 11.3 mmol) and **2d** (3.20 g, 14.7 mmol); yield: 65%; yellow oil.

IR (neat): ν = 1628, 1514, 1462, 1288, 1209 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.76 (t, 3 H, *J* = 7.0 Hz), 0.82 (t, 3 H, *J* = 7.0 Hz),2.68–3.20 (m, 3 H), 3.41–3.62 (m, 1 H), 3.68 (s, 3 H), 3.77 (s, 3 H), 6.51 (dd, 1 H, *J* = 2.4, 8.4 Hz), 6.61 (d, 1 H, *J* = 2.4 Hz), 7.03 (d, 1 H, *J* = 8.4 Hz), 7.25–7.40 (m, 4 H).

^{13}C NMR (DMSO-d_6): δ = 11.92, 13.49, 37.35, 41.49, 55.22, 55.32, 98.30, 104.36, 120.65, 126.08, 126.64, 127.78, 131.06, 131.30, 134.83, 137.31, 157.11, 160.21, 169.11.

MS (CI, 120 eV): *m/z* (%) = 314 (M^+H, 100), 241 (18).

N,N-Diethyl-2′,3′-dimethoxy-2-biphenylcarboxamide **(3e)**: from **1a** (2.00 g, 7.80 mmol) and **2e** (4.20 g, 14.7 mmol); yield: 48%; yellow oil.
IR (neat): ν = 1630, 1580, 1474, 1425, 1265 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 0.82 (t, 3 H, *J* = 7.4Hz), 0.95 (t, 3 H, *J* = 7.4 Hz), 2.75–3.38 (m, 3 H), 3.73 (s, 3 H), 3.64–3.83 (m, 1 H), 3.89 (s, 3 H), 6.90 (dd, 2 H, *J* = 1.0, 8.5 Hz), 7.02 (q, 1 H, *J* = 8.5 Hz), 7.34–7.44 (m, 4 H).
^{13}C NMR ($CDCl_3$):δ = 11.82, 13.71, 37.99, 42.37, 55.81, 60.96, 112.00, 123.24, 123.36, 126.24, 127.28, 127.95, 130.64, 133.97, 135.25, 137.17, 146.42, 152.67, 170.20.
MS (EI, 70 eV): *m/z* (%) = 313 (M^+, 26), 282 (100), 241 (54).

N-(2-Hydroxy-1,1-dimethyl)-3′,4′-dimethoxy-2-biphenylcarboxamide **(4)**: from 2-(2-bromophenyl)-4,4-dimethyloxazoline (**1b**; 3.20 g, 12.7 mmol) in THF (100 mL) and 4-bromoveratrole (**2a**; 4.10 g, 19.0 mmol) in DME (100 mL) and EtOH (4 mL). Purified by chromatography on silica gel (80% EtOAc in hexane); yield: 57%; white solid; mp 93–95 °C.
IR (KBr):ν = 3412, 3248, 1633 cm^{-1}.
^{1}HNMR (DMSO-d_6): δ = 1.11 (s, 3 H), 3.28 (d, 2 H, *J* = 6.1 Hz), 3.33 (s, 2 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.76 (t, 1 H, *J* = 6.1 Hz), 6.91–7.01 (m, 3 H), 7.30–7.47 (m, 5 H).
^{13}C NMR (DMSO-d_6): δ = 23.14, 54.78, 55.37, 55.58, 67.68, 111.58, 112.55, 120.77, 126.53, 127.70, 128.92, 129.61, 132.88, 137.84, 138.81, 148.24, 169.17.
MS (CI, 120 eV): *m/z* (%) = 330 (M^+H, 100), 241 (65).

3′,4′-Dimethoxy-2-biphenylcarboxylic Acid (5):
The amide **4** (2.00 g, 6.08 mmol) was added to 4.5 N HCl and the mixture heated at reflux for 16 h. After cooling to r.t., the solid precipitate was filtered and washed with H_2O (100 mL) to give **5**; yield: 1.10 g (70%); mp 161–163 °C (EtOH) (Lit.[21] mp 162–165 °C).
IR (KBr): ν = 3323, 1726, 1520, 1254 cm^{-1}.
^{1}HNMR ($CDCl_3$, 400 MHz): δ = 3.86 (s, 3 H), 3.91 (s, 3 H), 6.87–6.90 (m, 3 H), 7.37–7.43 (m, 2 H), 7.55 (m, 1 H), 7.91 (dd, 1 H, *J* = 1.1, 7.9 Hz), 8.36–12.20 (br, 1 H).
^{13}C NMR ($CDCl_3$): δ = 55.82, 55.85, 110.86, 112.00, 120.81, 126.94, 129.42, 130.49, 131.10, 131.95, 133.57, 142.81, 148.47, 148.54, 173.58.
MS (CI, 120 eV): *m/z* (%) = 259 (M^+H, 30), 258 (43), 241 (100).

1,3-Dimethoxyfluoren-9-one (6b); Typical Procedure:
To a stirred solution of LDA (13.5 mmol) in THF (50mL) was added **3b (**1.70 g, 5.42 mmol) in THF (20 mL) at –20 °C. The resulting solution was allowed to warm to r.t. and stirred 16 h. Satd aq NH_4Cl solution (30 mL) was added and the organic layer seperated. The aq NH_4Cl layer was extracted with THF (70 mL) and the combined organic layers were dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by chromatography on silica gel (40% EtOAc in hexane) to give **6b** (1.18 g, 4.91 mmol); yield: 91%; mp 143–144 °C (MeOH) (Lit.[22] mp 143–144°C).
IR (KBr): ν = 1690 cm^{-1}.
^{1}HNMR ($CDCl_3$, 400 Mhz): δ = 3.80 (s, 3 H), 3.87 (s, 3 H), 6.14 (d, 1 H, *J* = 2.0 Hz), 6.53 (d,1H, *J* = 1.9 Hz), 7.17–7.24 (m, 1 H), 7.31–7.36 (m, 2 H), 7.52 (d,1 H, *J* = 7.2 Hz).
^{13}C NMR (DMSO-d_6): δ = 55.72, 56.11, 98.41, 100.62, 112.61, 120.82, 122.63, 129.53, 133.69, 134.83, 141.81, 147.68, 159.67, 167.32, 188.99.
MS (CI, 120 eV): *m/z* (%) = 241 (M^+H, 100).

Using the above procedure, the following compounds were prepared:
1,2-Dimethoxyfluoren-9-one **(6a)**: from **3a** (1.79 g, 5.7 mmol) and LDA (13.7 mmol); yield: 84%; mp 113–115 °C (MeOH) (Lit.[23] mp 113–114 °C).
HRMS (FAB, M^+H): *m*/*z* calc.241.086469; found 241.086954.
IR (KBr): ν = 1709 cm^{-1}.
^{1}HNMR ($CDCl_3$, 400 MHz): δ = 3.89 (s, 3 H), 4.11 (s, 3 H), 6.93 (d, 1 H, *J* = 8.0 Hz), 7.16 (d, 1 H, *J* = 8.0 Hz), 7.19–7.25 (m, 1 H), 7.42–7.47 (m, 2 H), 7.62 (d, 1 H, *J* = 7.4 Hz).
^{13}C NMR (DMSO-d_6): δ = 56.25, 61.28, 116.40, 117.86, 120.24, 123.57, 124.23, 128.16, 133.73, 134.95, 136.04, 143.59, 148.28, 153.75, 190.62.

1,4-Dimethoxyfluoren-9-one **(6c)**: from **3c** (1.60 g, 5.1 mmol) and LDA (12.8 mmol); yield: 89%; mp 164–166 °C (MeOH) (Lit.[13b,24] mp 165–166 °C).
IR (KBr): ν = 1699 cm^{-1}.
^{1}HNMR ($CDCl_3$, 400 MHz): δ = 3.89 (s, 3 H), 3.91 (s, 3 H), 6.74 (d, 1 H, *J* = 9.1 Hz), 6.97 (d, 1 H, *J* = 9.1 Hz), 7.21 (t, 1 H, *J* = 7.6 Hz), 7.40 (t, 1 H, *J* = 7.6 Hz), 7.60 (d, 1 H, *J* = 7.6 Hz), 7.80 (d, 1 H, *J* = 7.6 Hz).
MS (CI, 120 eV): *m/z* (%) = 241 (M^+H, 100).
^{13}C NMR ($CDCl_3$): δ = 55.92, 56.13, 114.02, 120.15, 120.97, 123.54, 124.22, 128.13, 132.21, 133.89, 134.00, 142.41, 149.52, 152.37, 192.00.

2,4-Dimethoxyfluoren-9-one **(6d)**: from **3d** (1.2 g, 3.8 mmol) and LDA (10 mmol); yield: 76%; mp 144–146 °C (MeOH) (Lit.[13a,b] mp 116 °C).
IR (KBr): ν = 1713 cm^{-1}.
^{1}HNMR ($CDCl_3$, 400 MHz): δ = 3.83 (s, 3 H), 3.90 (s, 3 H), 6.53 (d, 1 H, *J* = 2.0 Hz), 6.81 (d, 1 H, *J* = 2.0 Hz), 7.11 (t, 1 H, *J* = 7.4 Hz), 7.37 (t, 1 H, *J* = 7.4 Hz), 7.54 (d, 1 H, *J* = 7.4 Hz), 7.63 (d, 1 H, *J* = 7.4 Hz).
^{13}C NMR (DMSO-d_6): δ = 55.85, 55.95, 101.27, 104.96, 122.81, 123.01, 123.75, 127.17, 132.73, 135.39, 135.70, 143.63, 156.08, 162.15, 193.04.
MS (EI, 70 eV): *m/z* (%) = 240 (M^+, 100).

3,4-Dimethoxyfluoren-9-one **(6e)**: from **3e** (1.0 g, 3.2 mmol) and LDA (7.9 mmol); yield: 78%; mp 141–143 °C (MeOH) (Lit.[22] mp 142.5 °C).
IR (KBr): ν = 1701 cm^{-1}.
^{1}HNMR ($CDCl_3$, 400 MHz): δ = 3.94 (s, 3 H), 3.96 (s, 3 H), 6.74 (d, 1 H, *J* = 8.1 Hz), 7.27 (t, 1 H, *J* = 7.2 Hz), 7.42 (d, 1 H, *J* = 8.1 Hz), 7.47 (t, 1 H, *J* = 7.2 Hz), 7.63 (d, 1 H, *J* = 7.2 Hz), 7.84 (d, 1 H, *J* = 7.2 Hz).
^{13}C NMR ($CDCl_3$): δ = 56.14, 60.37, 111.19, 121.36, 123.77, 123.91, 128.01, 128.71, 134.48, 135.13, 136.30, 142.42, 144.75, 159.06, 192.36.
MS (CI, 120 eV): *m/z* (%) = 241 (M^+H, 90), 258 (M^+NH_4).

2,3-Dimethoxyfluoren-9-one (6f): 3′,4′-Dimethoxy-2-biphenylcarboxylic acid (**5**; 1.3 g, 5.0 mmol) was dissolved in $CHCl_3$ (25 mL) and trifluoroacetic anhydride (TFAA, 5 mL, 35 mmol) added at r.t. After 30 min, the mixture was poured onto ice (30 g) and made basic with K_2CO_3. The mixture was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (40% EtOAc in hexane) to give **6f** (1.13 g, 4.7 mmol); yield: 94%; mp 162–164°C (MeOH) (Lit.[12] mp 164 °C).
IR (KBr): ν = 1705 cm^{-1}.
^{1}HNMR ($CDCl_3$, 400 MHz): δ = 3.91 (s, 3 H), 4.00 (s, 3 H), 6.98 (s, 1 H,), 7.17 (s,1 H), 7.18 (t, 1 H, *J* = 7.4 Hz), 7.33 (d, 1 H, *J* = 7.4 Hz), 7.39 (t, 1 H, *J* = 7.4 Hz), 7.53 (d, 1 H, *J* = 7.4 Hz).
^{13}C NMR ($CDCl_3$): δ = 56.22, 56.33, 103.39, 107.11, 119.07, 123.72, 126.84, 128.15, 134.18, 134.72, 139.45, 143.92, 149.71, 154.55, 193.12.
MS (EI, 70 eV): *m/z* (%) = 240 (M^+, 100).

1,2-Dihydroxyfluoren-9-one (7a); Typical Procedure:
1,2-Dimethoxyfluoren-9-one (**6a**; 1.05 g, 4.3 mmol) was added to 48% aq HBr (20 mL) and glacial AcOH (6 mL) and the mixture was

stirred at reflux 16 h. After cooling to r.t., the dark mixture was poured into H_2O (75 mL) and filtered through a sintered glass funnel. The solids were washed with H_2O (3 × 50 mL) and then with CH_2Cl_2 (50 mL). The solids were dissolved into EtOAc (100 mL) on a steam bath and the mixture filtered through Celite. The Celite was washed with hot EtOAc (100mL) and the combined organic washings were dried ($MgSO_4$). Filtration and evaporation of solvent under reduced pressure gave **7a**; yield: 0.57 g (62%); mp 187–189 °C (EtOH) (Lit.[25] mp 188–189 °C).
HRMS (FAB, M^+H): *m/z* calc. 213.055169; found 213.054350.
IR (KBr): ν = 1686 cm^{-1}.
^{1}HNMR (DMSO-d_6, 400 MHz): δ = 6.92 (d, 1 H, *J* = 7.8 Hz), 7.04 (d, 1 H, *J* = 7.8 Hz), 7.25 (t, 1 H, *J* = 7.7 Hz), 7.45–7.55 (m, 2 H), 7.59 (d, 1 H, *J* = 7.6 Hz), 9.49–10.37 (br, 2 H).
^{13}C NMR (DMSO-d_6): δ = 112.45, 118.69, 119.73, 119.86, 123.17, 127.54, 134.15, 134.35, 134.42, 144.00, 146.17, 191.83.

Using the above procedure, the following compounds were prepared:
1,3-Dihydroxyfluoren-9-one **(7b)**: from **6b** (1.10 g, 4.6 mmol); yield: 92%; mp 204–207 °C (EtOAc/hexane).
HRMS (FAB, M^+H): *m/z* calc. 213.055169; found 213.054405.
IR (KBr): ν = 1661 cm^{-1}.
^{1}HNMR (DMSO-d_6, 400 MHz): δ = 6.18 (d, 1 H, *J* = 1.8 Hz), 6.67 (d, 1 H, *J* = 1.8 Hz), 7.33 (t, 1 H, *J* = 7.4 Hz), 7.45–7.55 (m, 2 H), 7.65 (d, 1 H, *J* = 7.4 Hz), 9.36–11.33 (br, 2 H).
^{13}C NMR (DMSO-d_6): δ = 101.91, 102.98, 110.61, 120.41, 122.35, 129.11, 133.34, 135.37, 141.96, 147.09, 158.95, 165.71, 189.33.

1,4-Dihydroxyfluoren-9-one **(7c)**: from **6c** (1.10 g, 4.6 mmol); yield: 85%; mp >250 °C (EtOAc/hexane) (Lit.[24] mp 263–264 °C).
HRMS (FAB, M^+H): *m/z* calc. 213.055169; found 213.054611.
IR (KBr): ν = 1684 cm^{-1}.
^{1}HNMR (DMSO-d_6, 400 MHz): δ = 6.68 (d, 1 H, *J* = 8.8 Hz), 6.96 (d, 1 H, *J* = 8.8 Hz), 7.24 (t, 1 H, *J* = 6.8 Hz), 7.46–7.54 (m, 2 H), 7.81 (d, 1 H, *J* = 6.9 Hz), 9.77 (br, 1 H), 9.83 (s, 1 H).
^{13}C NMR (DMSO-d_6): δ = 117.88, 120.38, 123.03, 123.69, 126.58, 126.68, 127.63, 133.50, 134.31, 142.80, 146.29, 149.99, 191.76.

2,4-Dihydroxyfluoren-9-one **(7d)**: from **6d** (0.44 g, 1.8 mmol); yield: 79%; mp >250 °C (EtOAc/hexane).
HRMS (FAB, M^+H): *m/z* calc. 213.055169; found 213.054584.
IR (KBr): ν = 1697 cm^{-1}.
^{1}HNMR (DMSO-d_6, 400 MHz): δ = 6.49 (d, 1 H, *J* = 2.0 Hz), 6.52 (d, 1 H, *J* = 2.0 Hz), 7.14 (t, 1 H, *J* = 7.4 Hz), 7.43–7.51 (m, 2 H), 7.61 (d, 1 H, *J* = 7.4 Hz), 9.92 (s, 1 H), 10.33 (s, 1 H).
^{13}C NMR (DMSO-d_6): δ = 103.34, 108.85, 119.82, 122.28, 123.55, 126.28, 132.74, 135.30, 136.25, 144.73, 154.41, 159.83, 193.59.

3,4-Dihydroxyfluoren-9-one **(7e)**: from **6e** (0.42 g, 1.7 mmol); yield: 83%; mp 240–242 °C (dec.) (EtOAc/hexane) [Lit.[25] mp 240 °C (dec.)].
HRMS (FAB, M^+H): *m/z* calc. 213.055169; found 213.054277.
IR (KBr): ν = 1682 cm^{-1}.
^{1}HNMR (DMSO-d_6, 400 MHz): δ = 6.70 (d, 1 H, *J* = 7.7 Hz), 7.03 (d, 1 H, *J* = 7.7 Hz), 7.26 (t, 1 H, *J* = 7.2 Hz), 7.48–7.54 (m, 2 H), 7.80 (d, 1 H, *J* = 7.2 Hz), 9.24–11.22 (br, 2 H).
^{13}C NMR (DMSO-d_6): δ = 114.35, 117.19, 123.09, 123.62, 125.86, 127.87, 129.17, 134.25, 134.51, 142.09, 142.95, 153.35, 191.84.

2,3-Dihydroxyfluoren-9-one **(7f)**: from **6f** (0.50 g, 2.1 mmol); yield: 90%; mp 239–241 °C (EtOAc/hexane) (Lit.[24] mp 237–238 °C).
HRMS (FAB, M^+H): *m/z* calc. 213.055169; found 213.054440.
IR (KBr): ν = 1695 cm^{-1}.
^{1}HNMR (DMSO-d_6, 400 MHz): δ = 6.97 (s, 1 H), 7.09 (s, 1 H), 7.21 (t, 1 H, *J* = 7.2 Hz), 7.40–7.53 (m, 3 H), 9.04–10.79 (br, 2 H).
^{13}C NMR (DMSO-d_6): δ = 108.70, 111.23, 119.56, 122.90, 125.15, 127.84, 134.31, 134.49, 137.65, 143.88, 146.11, 152.22, 192.14.

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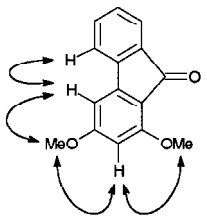
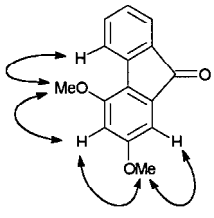
(1) Sill, A. D.; Albrecht, W. L.; Andrews, E. R.; Fleming R. W.; Horgan, S. W.; Roberts, E.M.; Sweet, F.W. *J. Med. Chem.* **1973**, *16*, 240.
(2) Ray, F. E.; Rieveschl, G. *J. Am. Chem. Soc.* **1943**, *65*, 836.
(3) Pan, H. L.; Fletcher, T. L. *J. Med. Chem.* **1965**, *8*, 491.
(4) Sargent, M. V. *J. Chem. Soc., Perkin Trans.1* **1987**, 2553.
(5) Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424.
(6) Jones, W. D.; Ciske, F. L. *J. Org. Chem.* **1996**, *61*, 3921.
(7) Gould, S. J.; Chen, J.; Cone, M. C.; Gore, M. P.; Melville, C. R.; Tamayo, N. *J. Org. Chem.* **1996**, *61*, 5720.
(8) Hauser, F. M.; Zhou, M. *J. Org. Chem.* **1996**, *61*, 5722.
(9) Mohri, S.-i.; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072.
(10) Jones, W. D.; Ciske, F. L. Unpublished results.
(11) Reiveschl, G.; Ray, F. E. *Chem. Rev.* **1938**, *23*, 287.
(12) Pol, V. A.; Wagh, S. M.; Barve, V. P.; Kulkarni, A. B. *Indian J. Chem.* **1969**, *7*, 557.
(13) a) Ramana, M. M. V.; Potnis, P. V. *Synthesis* **1993**, 575.
b) Observed NOE's for structural confirmation.



6b



6d

(14) Fu, J.-m.; Zhao, B.-p.; Sharp, M. J.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 1683.
(15) a) Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501.
b) Giroux, A.; Han, Y.; Prasit, P. *Tetrahedron Lett.* **1997**, *38*, 3841.
(16) A similar ring-opened product was previously reported. See Altman, J.; Bohnke, H.; Steigel, A.; Wulff, G. *J Organomet. Chem.* **1986**, *309*, 241.
(17) 2% isolated yield of 1,2-dimethoxyfluoren-9-one.
(18) Chew, W.; Hynes, R. C.; Harpp, D. N. *J. Org. Chem.* **1993**, *58*, 4398.
(19) a) McCabe, E. T.; Barthel, W. F.; Gertler, S. I.; Hall, S. A. *J. Org. Chem.* **1954**, *19*, 493.
b) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787.
(20) Subramanian, L. R.; Hanack, M.; Chang, L. W. K.; Imhoff, M. A.; Schleyer, P. v. R.; Effenberger, F.; Kurtz, W.; Stang, P. J.; Dueber, T. E. *J. Org. Chem.* **1976**, *41*, 4099.
(21) Jeffs, P. W.; Archie, W. C.; Hawks, R. L.; Farrier, D. S. *J. Amer. Chem. Soc.* **1971**, *93*, 3752.
(22) Sato, M.; Uchida, A.; Tsunetsugu, J.; Ebine, S. *Tetrahedron Lett.* **1977**, 2151.
(23) Nakano, J.; Katagiri, N.; Kato, T. *Chem Pharm. Bull.* **1982**, *30*, 2590.
(24) Koelsch, C. F.; Flesch, R. N. *J. Org. Chem.* **1955**, *20*, 1270.
(25) Horner, L.; Baston, D. W. *J. Liebigs Ann. Chem.* **1973**, 910.