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# A Convenient Preparation of Xanthene Dyes

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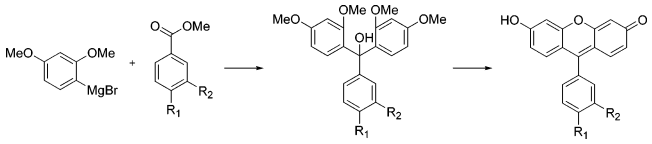

A facile synthetic route utilizing readily available reagents affords a series of regioisomerically pure xanthene dye derivatives. Advantages include relatively mild conditions and good to excellent yields. Nonpolar, highly crystalline intermediates are isolable by standard chromatographic techniques. The intermediates are in the requisite xanthene oxidation state, thus avoiding the need for relatively inefficient oxidation chemistry and/or harsh conditions. During the course of this work, a new boron-mediated 1,2-aryl migration reaction was discovered.

## Introduction

Fluorescein and fluorone are structurally related xanthene dyes (Figure 1). Fluorone is formally decarboxylated fluorescein. Fluorone derivatives have found numerous applications. They have been used in the detection of a variety of metal ions,[1] sugars,[2] phosphorylated molecules,[3] HIV-1 nucleocapsid protein,[4] reactive oxygen species,[5] in screening assays for mitochondrial permeability,[6] acetylcholinesterase inhibition,[7] and telomerase inhibition.[8] We have reported the use of fluorones as sialic acid[9] and homocysteine probes.[10]

The initial fluorone synthesis was reported by Mohlau and Koch.[11] Typical syntheses include the following sequence: (i) formation of the leuco base via the condensation of resorcinol with aldehydes under thermal and acid-catalyzed conditions and (ii) the formation of dye via the oxidation of the leuco base. It has been reported that the oxidation step is often low-yielding. Additionally, there can be purification problems due to the formation of byproducts and the relatively polar nature of fluorone derivatives.[12]

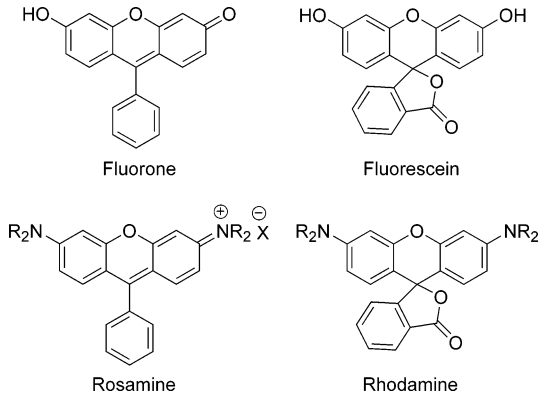


**FIGURE 1.** Structures of some common xanthene dyes.

Recently, a novel and innovative microwave protocol resulted in improved yields in related rosamine derivative syntheses.[12d] The microwave-assisted condensation

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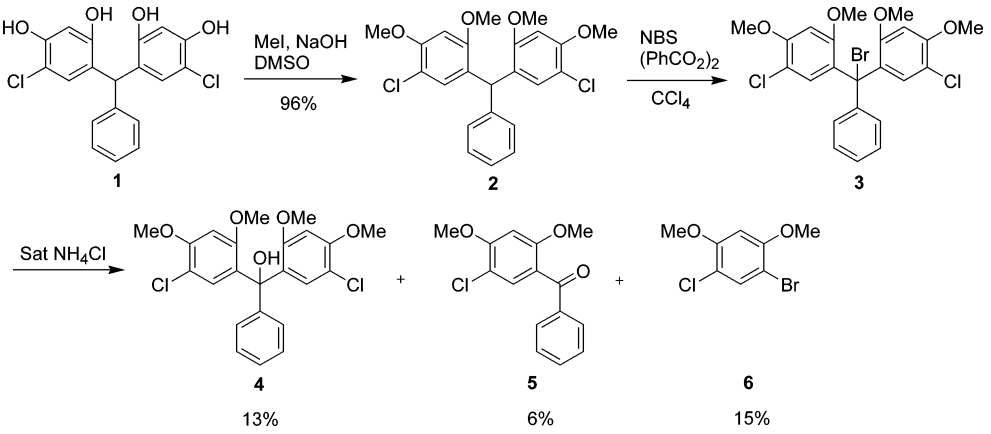
**SCHEME 1**




and oxidation gave relatively higher yields (typically ranging from 27 to 73%) than traditional thermal condition (typical ranges from 8 to 35%).

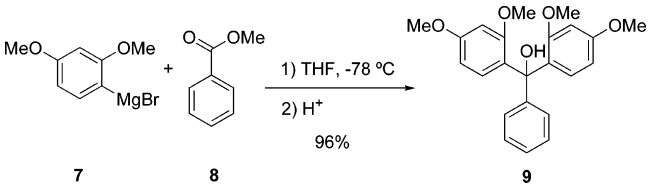
Fluorone dye preparations have also been reported earlier by Neckers et al. as part of his extensive and pioneering work on xanthenes, involving heating intermediates in a sealed tube at 200 °C.[13] Benzophenones have also been used as condensation partners in high-temperature, acid-catalyzed syntheses of xanthenes.[14] A novel oxidation reaction of substituted triphenylmethanes has been reported to occur via $Br_2/CCl_4$.[15]

Herein, we report a simple new protocol for attaining a series of fluorone derivatives. It is based on forming tertiary carbinol leuco bases via Grignard reactions. Treatment of carbinol leuco bases with $BBr_3$ affords the desired dyes. The carbinol intermediate is much less polar than the dye products. It can thus be purified via standard column chromatography. These intermediates are often highly crystalline (vide infra). The carbinol carbon is already in the correct oxidation state of the desired dyes. Therefore, potentially troublesome oxidations are avoided. The dye products can be purified by simple filtration methods without chromatography. The use of low-temperature, basic conditions may serve as an attractive alternative to more common, relatively harsh acid-catalyzed and oxidative methods. In addition, during the course of this work we discovered a novel 1,2-aryl migration mediated by boron that furnishes potentially useful dendrimer cores as well as dye architectures.

## Results and Discussion

In our initial investigations, we use free radical bromination of appropriate triaryls as a means to obtain dye precursors with the requisite oxidation state. Tetramethyl ether **2** is obtained in nearly quantitative yield by stirring **1**[16] via known procedures.[17] Compound **2** (500 mg in 20 mL of $CCl_4$) is treated with NBS (1.05 equiv) in the presence of a catalytic amount of $(PhCO_2)_2$ in $CCl_4$ (Scheme 1).

**SCHEME 2**




Upon washing the crude brominated product with a saturated $NH_4Cl$ solution, carbinol **4** is obtained in a 13% yield. Reverse condensation product 5 and brominated congener **6** are also obtained in 6% and 15% yields, respectively. The mechanism of resorcinarene reverse condensation has previously been studied in great detail.[12c,18] Compounds **5** and **6** were synthesized independently.[19] The structures of **1**, **2**, **4**, **5**, and **6** are verified by single-crystal X-ray structural analysis (Supporting Information).

Since solvolysis of bromide **3** occurs readily during workup,[15] we decided to synthesize the carbinol precursor directly. It is conveniently accessed by the reaction of readily available Grignard reagents and esters. Compound **9** is obtained in one step in a yield of 96% by reacting 2,4-dimethoxybenzenemagnesium bromide **7** and methyl benzoate **8** (Scheme 2). The structure of **9** is confirmed by X-ray crystallography (Supporting Information). When **9** is treated with $BBr_3$ (6 equiv), monomethyl ether **10** is obtained in 64% yield. Using a greater excess of $BBr_3$ (16 equiv) furnishes fully deprotected **11** in a 65% yield. Compound **11** is conveniently isolated by filtration (Scheme 3).

It is straightforward to apply the above protocol to the synthesis of a series of regioisomerically pure fluorone dyes. When various methyl benzoates **12a**−**e** are used, the corresponding carbinols **13a**−**e** are obtained in excel-

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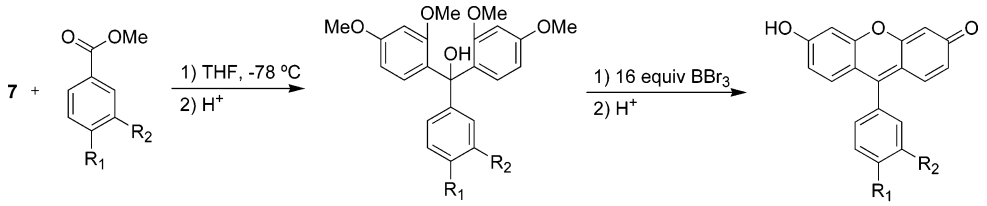
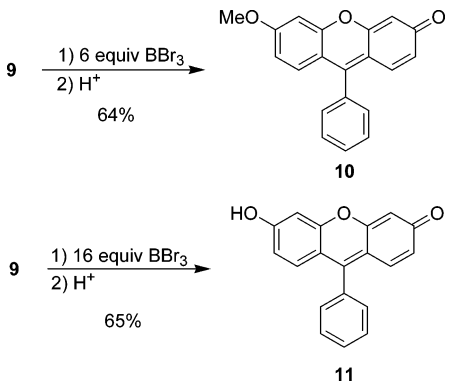
(19) Detailed synthetic route is described in the Experimental Section.

**TABLE 1.**




| entry | substrate | $R_1$ | $R_2$ | carbinol | carbinol yield (%) | fluorone | fluorone yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **12a** | Br | H | **13a** | 92 | **14a** | 70 |
| 2 | **12b** | Ph | H | **13b** | 99 | **14b** | 87 |
| 3 | **12c** | OMe | H | **13c** | 83 | **14c** | 96 |
| 4 | **12d** | H | $NO_2$ | **13d** | 91 | **14d** | 73 |
| 5 | **12e** | $NO_2$ | H | **13e** | 95 | | |

**SCHEME 3**




lent yields (>90%). The reaction of the carbinols **13a**−**d** with 16 equiv of $BBr_3$ furnishes the corresponding fluorone dyes with yields ranging from 70 to 88% while deprotection of **13e** affords methyl ether **15** (Table 1). Compound **15** is completely deprotected using 20 equiv of $BBr_3$ to furnish **14e** in a 76% yield (Scheme 4). In each case, the fluorone products are obtained without preparative chromatography. The structures of **13b** and **13e** are confirmed by single-crystal X-ray structure analysis (Supporting Information).

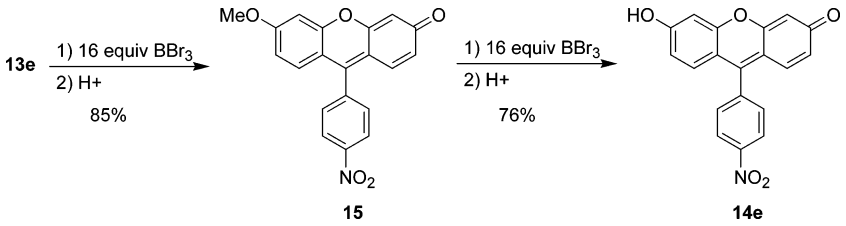
To prepare a potential sialic acid sensor **16**,[9] carbinol **17** was targeted (Scheme 5).

The reaction of **7** (2.4 equiv) and **18** (1 equiv), however, affords compound **19** in 13% yield. When 3.6 equiv of **7** is used, the yield of **19** improves to 32%. In each run, 2,4-dimethoxyphenylboronic acid **20** is isolated in trace amounts (Scheme 6). Structures of **18**, **19** (Figure 2), and **20** were confirmed by single-crystal X-ray structure analysis (Supporting Information).

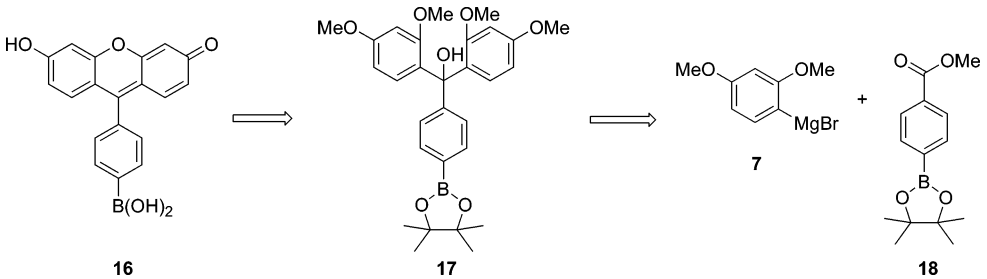
A proposed mechanism for the formation of compound **19** is shown in Scheme 7. The first equivalent of **7** reacts with boron to form the tetrahedral anionic boronate **21**. This is supported by the fact that **18** is quantitatively recovered when 1 equiv of **7** is added to a solution of **18** and stirred overnight before quenching with water. The second and third equivalents of **7** react with the ester to afford the tertiary oxide **22**. Upon workup, a 1,2-aryl shift mediated by boron affords **19**.

1,2-Alkyl shifts have been known for decades.[20] In 1963, Matteson described the prototypical 1,2-alkyl shift involving α-haloalkyl borates.[21] Negishi and co-workers established the analogous 1,2-rearrangement of 1-chloroalkyl complexes of Al, Mg, Zn, Cd, Ti, Zr, Hf, V, Cr, Mn, Fe, Co, Ni, and Cu.[22] It has also been found that organoboronate complexes bearing α,β-unsaturation and

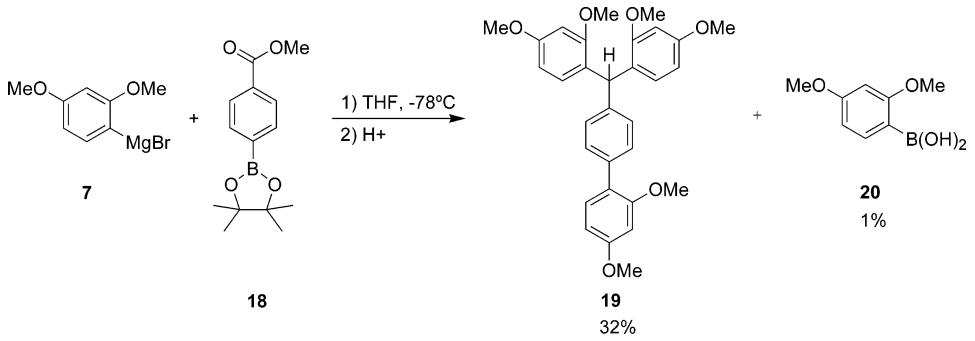
**SCHEME 4**



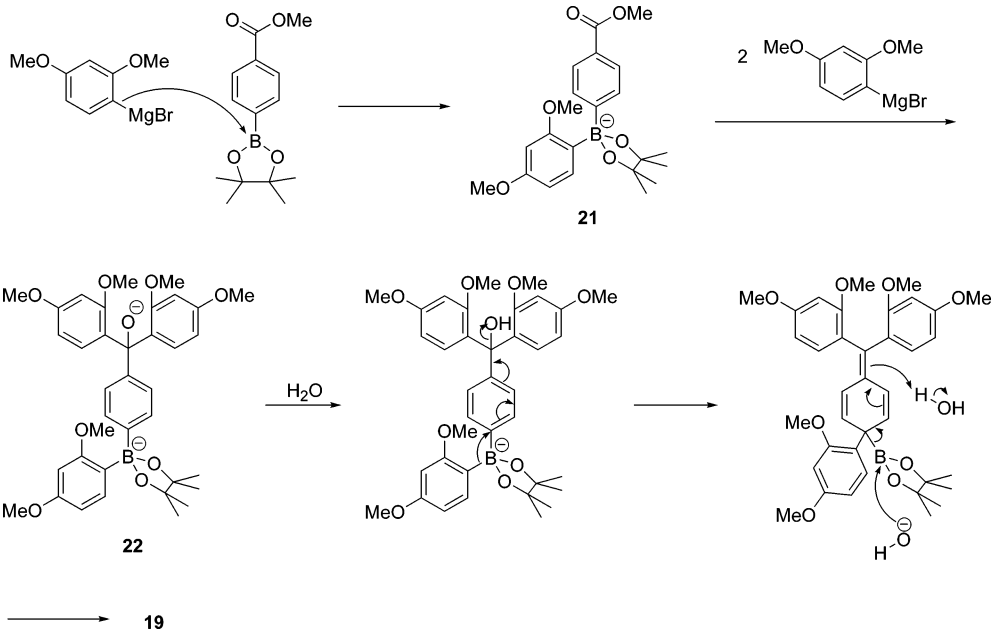

**SCHEME 5**



**SCHEME 6**




**SCHEME 7**




leaving groups at the α- and γ-carbons can undergo a 1,2-alkyl group migration to afford homologated organoboron compounds.[23] A recent article described a transformation whereby an organozincate bearing a leaving group at the remote benzylic position would rearrange with concomitant carbon−carbon bond formation to furnish the benzylzincate[22j,24] (Scheme 8). In the current case (Scheme 7), the boronic acid is not found in the final product. This

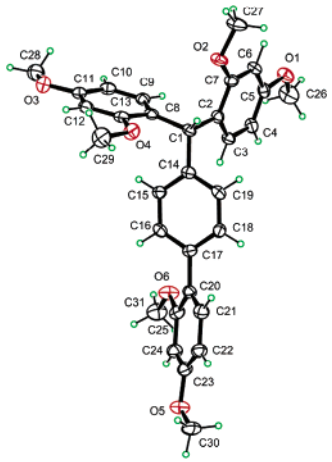
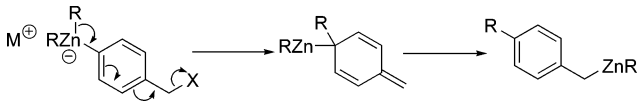



**FIGURE 2.** X-ray structure for **19**.

**SCHEME 8**[22j]




is the first observation of a 1,2-aryl group migration mediated by an arylboronate complex involving a leaving group at a remote benzylic position. Compound **19** and congeners may serve as functional dye and/or dendrimer substrates.

## Conclusion

Carbinol leuco bases are easily prepared and purified precursors for fluorone dyes. A novel reaction that involves a boron-mediated 1,2-aryl shift reaction with a leaving group at a remote benzylic position is described. The methods described herein are now being utilized in our lab toward the synthesis of new naphthofluorescein dye architectures currently unattainable via other methodologies.

## Experimental Section

**5,5′-Dichloro-2,2′,4,4′-tetramethoxytrityl Alcohol (4).** In a 50-mL round-bottom flask, compound **2** (0.500 g, 1.18 mmol) and NBS (0.315 g, 1.77 mmol) are dissolved in 20 mL of $CCl_4$.

A catalytic amount of benzoyl peroxide (~10 mg) is added. The reaction mixture is heated at reflux for 1 h with vigorous stirring. It is cooled to room temperature and quenched with 50 mL of saturated $NH_4Cl$ (aq). The mixture is extracted with $CH_2Cl_2$ (3 × 15 mL). The combined extracts are dried over $MgSO_4$ and filtered, and the filtrate is evaporated to dryness. The solid residue is purified by flash column chromatography (silica gel; $CH_2Cl_2$) to give 72 mg (14%) of **4** along with 18 mg (6%) of **5** and 43 mg (15%) of **6**. The structures of **5** and **6** were verified via independent syntheses (vide infra). Data for **4**: $^1$H NMR (DMSO-$d_6$, 250 MHz) $\delta$ 7.23−7.16 (m, 5H), 7.05 (s, 2H), 6.76 (s, 2H), 5.52 (s, 1H), 3.88 (s, 6H); $^{13}$C NMR (DMSO-$d_6$, 62.9 MHz) $\delta$ 156.6, 154.4, 146.0, 129.0, 127.3, 127.3, 127.0, 126.4, 111.3, 98.8, 78.0, 56.2, 55.9. MALDI-TOF *m/z* 431.517 $[M - OH]^+$, 447.544 $[M]^+$.

**5-Chloro-2,4-dimethoxybenzophenone (5).** A 20-mL volume of $CH_3CN$ solution containing 2,4-dimethoxybenzophenone (0.500 g, 2.07 mmol) and NCS (0.200 g, 2.17 mmol) is mixed with 100 mg of 60 Å silica gel. The reaction mixture is heated at reflux for 5 h with vigorous stirring and cooled to room temperature. Silica gel is removed via suction filtration, and $CH_3CN$ is removed under reduced pressure. The residue is purified by flash column chromatography (silica gel; $CH_2Cl_2$) to afford 0.470 g (82%) of **5**. $^1$H NMR (DMSO-$d_6$, 250 MHz) $\delta$ 7.68−7.60 (m, 3H), 7.52−7.70 (m, 2H), 7.39 (s, 1H), 6.89 (s, 1H), 3.97 (s, 3H), 3.69 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 62.9 MHz) $\delta$ 193.6, 157.7, 157.6, 137.6, 133.1, 130.1, 129.1, 128.5, 121.0, 112.5, 98.1, 56.6, 56.2. MALDI-TOF *m/z* 276.1 $[M]^+$, 277.4 $[M + H]^+$, 299.0 $[M + Na]^+$, 314.9 $[M + K]^+$.

**1-Bromo-5-chloro-2,4-dimethoxy-benzene (6).** This compound was prepared following the procedures above for compound **5** except that 2,4-dimethoxybromobenzene (1.507 g, 6.9 mmol) is used instead of 2,4-dimethoxybenzophenone. The yield of **6** (1.22 g) is 70%. $^1$H NMR (DMSO-$d_6$, 250 MHz) $\delta$ 7.55 (d, $J$ = 1.2 Hz, 1H), 6.83 (d, $J$ = 1.2 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 62.9 MHz) $\delta$ 155.4, 155.0, 132.1, 112.7, 100.5, 98.6, 56.6, 56.5. MALDI-TOF *m/z* 247.890 $[M]^+$.

**2,2′,4,4′-Tetramethoxytrityl Alcohol (9).** Magnesium turnings (0.543 g, 22.3 mmol) and a few crystals of $I_2$ are placed in a 250-mL three-neck round-bottom flask fitted with a dropping funnel and a condenser. A solution of 2,4-dimethoxybromobenzene (5.0 g, 23.0 mmol) in 20 mL of anhydrous THF is added dropwise to the magnesium. The mixture is stirred for 20−30 min. The resulting Grignard reagent (2,4-dimethoxyphenylmagnesium bromide) is cooled in a dry ice/acetone bath before a solution of methyl benzoate (1.25 g, 9.38 mmol) in 40 mL of dry THF is added dropwise. The mixture is stirred overnight and then quenched with 100 mL of distilled water and neutralized with 2 N HCl. The unreacted 2,4-dimethoxybromobenzene as well as THF are removed by steam distillation. The resulting mixture is extracted with $CH_2Cl_2$ (3 × 30 mL). The combined extracts are dried over $MgSO_4$ and filtered, and the filtrate is evaporated to dryness. The residue is purified by flash chromatography (silica gel; EtOAc−hexane, 20:80) to afford 3.49 g (96%) of **9**. Compound **9** was prepared previously via other methodology.[25] NMR data is in agreement with the assigned structure: $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 7.21−7.10 (m, 5H), 6.86 (d, $J$ = 8.6 Hz, 2H), 6.52 (d, $J$ = 2.2 Hz, 2H), 6.42 (dd, $J$ = 8.6, 2.2 Hz, 2H), 5.17 (s, 1H), 3.73 (s, 6H), 3.40 (s, 6H); $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 159.7, 157.9, 147.4, 129.2, 127.4, 126.7, 127.9, 104.1, 99.5, 79.1, 55.4, 55.1.

**9-Phenyl-6-methoxy-3-fluorone (10).** A solution of **8** (0.178 g, 0.468 mmol) in 10 mL of dry $CH_2Cl_2$ is cooled to −78 °C using a dry ice/acetone bath before $BBr_3$ (0.935 g, 3.74 mmol) is added dropwise. The mixture is allowed to warm to room temperature gradually before being quenched with 20 mL of distilled $H_2O$. The mixture is extracted with $CH_2Cl_2$ (3 × 10 mL). The combined extracts are dried over $MgSO_4$ and filtered, and the filtrate is concentrated under reduced pressure. The residue is purified by flash chromatography (silica gel, EtOAc), affording 90 mg (64%) of **10**. $^1$H NMR (DMSO-$d_6$, 250 MHz) $\delta$ 7.63−7.61 (m, 3H), 7.47−7.43 (m, 2H), 7.21 (d, $J$ = 2.4 Hz, 1H), 7.08 (d, $J$ = 9.0 Hz, 1H), 7.01 (d, $J$ = 9.7 Hz, 1H), 6.94 (dd, $J$ = 9.0, 2.4 Hz, 1H), 6.42 (dd, $J$ = 9.7, 1.8 Hz, 1H), 6.21 (d, $J$ = 1.8 Hz, 1H), 3.90 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 62.9 MHz) $\delta$ 183.8, 164.1, 158.4, 154.0, 149.2, 132.4, 130.8, 129.7, 129.6, 129.5, 129.4, 128.8, 117.0, 113.9, 113.6, 104.7, 100.6, 56.3. MALDI-TOF *m/z* 303.154 $[M + H]^+$.

**9-Phenyl-6-hydroxy-3-fluorone (11).** To a stirred solution of **8** (0.400 g, 1.05 mmol) in 10 mL of dry $CH_2Cl_2$ at −78 °C, $BBr_3$ (4.20 g, 16.8 mmol) is added dropwise. The mixture is warmed to room temperature gradually before being quenched with 20 mL of distilled $H_2O$. After being stirred for 20 min, filtration leads to a collection of a red precipitate (**11**). A sample for analytical purposes is obtained by flash chromatography (silica gel, EtOAc−MeOH 9:1). A quantity of 197 mg (65%) of **11** is collected. Compound **11** is known; however, no characterization data was previously reported via the older synthetic methods.[26] $^1$H NMR (DMSO-$d_6$, 250 MHz) $\delta$ 7.63−7.60 (m, 3H), 7.46−7.43 (m, 2H), 7.01 (d, $J$ = 9.2 Hz, 2H), 6.60 (dd, $J$ = 9.2, 2.1 Hz, 2H) 6.60 (d, $J$ = 2.1 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$, 62.9 MHz) $\delta$ 156.3, 149.8, 132.5, 130.5, 129.5, 129.3, 128.8, 114.6, 103.4.

**2,2′,4,4′-Tetramethoxy-4″-bromotrityl Alcohol (13a).** This compound was prepared following the protocol described above for compound **9** except that 4-bromo methyl benzoate **12a** (2.01 g, 9.38 mmol) was used as the ester. The yield of **13a** (3.97 g) is 92%. $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 7.25 (d, $J$ = 8.5 Hz, 2H), 6.94 (d, $J$ = 8.5 Hz, 2H), 6.83 (d, $J$ = 8.6 Hz, 2H), 6.42 (d, $J$ = 2.0 Hz, 2H), 6.34 (dd, $J$ = 8.6, 2.0 Hz, 2H), 5.17 (s, 1H), 3.63 (s, 6H), 3.32 (s, 6H); $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 159.9, 157.8, 147.2, 129.7, 129,4, 129.1, 125.9, 118.9, 104.2, 99.4, 78.5, 55.3, 55.1. MALDI-TOF *m/z* 457.880 $[M]^+$, 441.521 $[M - OH]^+$, 481.532 $[M + K]^+$.

**2,2′,4,4′-Tetramethoxy-4″-phenyltrityl Alcohol (13b).** This compound is prepared following the procedure described above for compound **9** except that 4-phenyl methyl benzoate **12b** (1.13 g, 5.33 mmol) is used. The yield of **13b** (2.43 g) is 99%. $^1$H NMR (DMSO-$d_6$, 250 MHz) $\delta$ 7.64 (d, $J$ = 7.6 Hz, 2H), 7.47 (d, $J$ = 8.4 Hz, 2H), 7.43 (t, $J$ = 7.8 Hz, 2H), 7.32 (t, $J$ = 7.1 Hz, 1H), 7.19 (d, $J$ = 8.4 Hz, 2H), 6.93 (d, $J$ = 8.6 Hz, 2H), 6.55 (d, $J$ = 2.3 Hz, 2H), 6.45 (dd, $J$ = 8.6, 2.3 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$, 62.9 MHz) $\delta$ 159.7, 157.9, 146.7, 140.0, 137.6, 129.2, 128.9, 128.1, 127.1, 126.6, 126.5, 125.0, 104.1, 99.5, 78.9, 55.4, 55.1. MALDI-TOF *m/z* 439.654 $[M - OH]^+$, 479.599 $[M + Na]^+$.

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**2,2′,4,4′-Tetramethoxy-4″-methoxytrityl Alcohol (13c).** This compound is prepared following the procedures described above for compound **9** except that 4-methoxy methyl benzoate **12b** (1.55 g, 9.38 mmol) is used. The yield of **13c** (3.2 g) is 83%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.16 (d, $J$ = 6.9 Hz, 2H), 6.83 (d, $J$ = 8.6 Hz, 2H), 6.79 (d, $J$ = 6.9 Hz, 2H), 6.49 (d, $J$ = 2.4 Hz, 2H), 6.37 (dd, $J$ = 8.6, 2.4 Hz, 2H), 3.79 (s, 9H), 3.54 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 160.3, 158.7, 158.3, 139.7, 130.4, 129.1, 127.6, 112.7, 103.8, 100.2, 80.6, 55.9, 55.5, 55.4. MALDI-TOF *m/z* 409.490 $[M]^+$.

**2,2′,4,4′-Tetramethoxy-3″-nitrotrityl Alcohol (13d).** This compound is prepared following the procedure described above for compound **9** except that 3-nitro methyl benzoate **12d** (1.70 g, 9.38 mmol) is used. The yield of **13d** (3.86 g) is 95%. $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.00−7.98 (m, 2H), 7.55−7.42 (m, 2H), 7.08 (d, $J$ = 8.5 Hz, 2H), 6.54 (d, $J$ = 1.9 Hz, 2H), 6.50 (dd, $J$ = 8.5, 1.9 Hz, 2H), 5.59 (s, 1H), 3.75 (s, 6H), 3.39 (s, 6H); $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 160.2, 157.6, 150.3, 146.7, 134.2, 129.1, 127.8, 125.0, 122.0, 120.7, 104.4, 99.4, 78.1, 55.1. MALDI-TOF *m/z* 424.481 $[M]^+$, 448.565 $[M + Na]^+$, 464.538 $[M + K]^+$.

**2,2′,4,4′-Tetramethoxy-4″-nitrotrityl Alcohol (13e).** This compound is prepared following the procedure described above for compound **9** except that 4-nitro methyl benzoate **12e** (1.70 g, 9.38 mmol) is used. The yield of **13e** (3.51 g) is 91%. $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.04 (d, $J$ = 8.9 Hz, 2H), 7.35 (d, $J$ = 8.9 Hz, 2H), 7.06 (d, $J$ = 8.4 Hz, 2H), 6.54 (d, $J$ = 2.4 Hz, 2H), 6.49 (dd, $J$ = 8.4, 2.4 Hz, 2H), 5.53 (s, 1H), 3.75 (s, 6H), 3.40 (s, 6H); $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 160.2, 157.6, 155.9, 145.4, 129.0, 128.6, 124.9, 121.7, 104.4, 99.4, 78.2, 55.1. MALDI-TOF *m/z* 424.701 $[M]^+$, 408.624 $[M - OH]^+$.

**9-(4-Bromophenyl)-6-hydroxy-3-fluorone (14a).** This compound was prepared following the procedure above for compound **11** except that compound **13a** (0.400 g, 0.871 mmol) is used. The yield of **14a** (223 mg) is 70%. $^1$H NMR (DMSO-$d_6$, 250 MHz) $\delta$ 7.88 (d, $J$ = 7.5 Hz, 2H), 7.47 (d, $J$ = 7.5 Hz, 2H), 7.29 (d, $J$ = 9.4 Hz, 2H), 6.90 (d, $J$ = 2.1 Hz, 2H), 6.88 (dd $J$ = 9.4, 2.1 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$, 62.9 MHz) $\delta$ 172.1, 158.0, 132.5, 131.9, 131.7, 124.2, 120.9, 115.6, 102.8. MALDI-TOF *m/z* 367.228 $[M + H]^+$.

**9-(4-Biphenyl)-6-hydroxy-3-fluorone (14b).** This compound is prepared following the procedure above for compound **11** except that compound **22** (0.500 g, 1.09 mmol) is used. The yield of **14b** (330 mg) is 87%. $^1$H NMR (DMSO-$d_6$, 250 MHz) $\delta$ 7.91 (d, $J$ = 7.8 Hz, 2H), 7.79 (d, $J$ = 7.9 Hz, 2H), 7.55−7.49 (m, 5H), 7.09 (d, $J$ = 9.0 Hz, 2H), 6.59 (dd, $J$ = 9.0, 2.2 Hz, 2H), 6.54 (d, $J$ = 2.2 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$, 62.9 MHz) $\delta$ 157.2, 150.4, 141.9, 140.1, 132.6, 131.4, 131.0, 130.0, 128.9, 127.8, 127.7, 122.6, 115.0, 104.3. MALDI-TOF *m/z* 365.312 $[M + H]^+$, 387.322 $[M + Na]^+$.

**9-(4-Hydroxyphenyl)-6-hydroxy-3-fluorone (14c).** This compound is prepared following the procedure above for compound **11** except that compound **13c** (1.26 g, 3.07 mmol) is used. The yield of **14c** (900 mg) is 96%. $^1$H NMR ($CDCl_3$, 250 MHz) $\delta$ 10.07 (s, 1H), 7.25 (d, $J$ = 8.2 Hz, 2H), 7.14 (d, $J$ = 9.2 Hz, 2H), 6.98 (d, $J$ = 8.2 Hz, 2H), 6.59 (d, $J$ = 9.4 Hz, 2H), 6.52 (s, 2H); $^{13}$C NMR ($CDCl_3$, 62.9 MHz) $\delta$ 158.6, 156.4, 150.4, 131.1, 130.8, 122.6, 115.5, 114.6, 105.5, 103.3. MALDI-TOF *m/z* 305.127 $[M + H]^+$, 327.100 $[M + Na]^+$, 341.221 $[M + K]^+$.

**9-(3-Nitro-phenyl)-6-hydroxy-3-fluorone (14d).** This compound is prepared following the procedure above for compound **11** except that compound **14d** (0.480 g, 1.13 mmol) is used. The yield of **14d** (274 mg) is 73%. $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.42 (d, $J$ = 7.0 Hz, 1H), 8.26 (s, 1H), 7.89 (m, 2H), 6.96 (d, $J$ = 9.1 Hz, 2H), 6.55 (dd, $J$ = 9.1, 2.9 Hz, 2H), 6.53 (d, $J$ = 2.9 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$, 62.9 MHz) $\delta$ 156.3, 138.0, 147.0, 136.0, 134.3, 130.5, 130.3, 124.3, 114.3, 103.5. MALDI-TOF *m/z* 334.186 $[M + H]^+$, 356.167 $[M + Na]^+$.

**9-(4-Nitrophenyl)-6-hydroxy-3-fluorone (14e).** This compound was prepared following the procedure above for compound **11** except that compound **15** (30 mg) is used. The eluent for flash chromatography is EtOAc−MeOH 8:2. The yield of **14e** (21 mg) is 76%. $^1$H NMR (DMSO-$d_6$, 250 MHz) $\delta$ 8.44 (d, $J$ = 8.6 Hz, 2H), 7.46 (d, $J$ = 8.6 Hz, 2H), 6.90 (dd, $J$ = 8.9, 1.1 Hz, 2H), 6.54 (d, $J$ = 8.9 Hz, 2H), 6.52 (d, $J$ = 1.1 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$, 62.9 MHz) $\delta$ 174.8, 156.3, 148.0, 147.3, 139.7, 131.0, 130.1, 123.4, 122.1, 113.5, 103.6. MALDI-TOF *m/z* 334.273 $[M + H]^+$, 356.301 $[M + Na]^+$.

**9-(4-Nitrophenyl)-6-methoxy-3-fluorone (15).** This compound is prepared following the procedure above for compound **11** except that compound **13e** (0.500 g, 1.18 mmol) is used. The yield of **15** (346 mg) is 85%. $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 8.46(d, $J$ = 8.6 Hz, 2H), 7.25 (d, $J$ = 2.3 Hz, 1H), 7.07 (d, $J$ = 9.4 Hz, 1H), 6.98(d, $J$ = 9.8 Hz, 1H), 6.93 (dd, $J$ = 9.4, 2.3 Hz, 1H), 6.44 (dd, $J$ = 9.8, 1.8 Hz, 1H), 6.26 (d, $J$ = 1.8 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$, 75.5 MHz) $\delta$ 183.8, 164.3, 158.2, 154.0, 148.2, 139.3, 131.1, 130.5, 129.8, 129.5, 127.1, 124.0, 123.2, 117.2, 113.68, 113.4, 105.0, 100.8, 56.4. MALDI-TOF *m/z* 348.419 $[M + H]^+$.

**Bis-(2,4-Dimethoxyphenyl)-4-(2, 4-dimethoxyphenyl)-phenyl Methane (19).** This compound is prepared following the procedure described above for compound **9** except that **18** (1.64 g, 6.26 mmol) is used. The yield of **19** (1.00 g) is 32%. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.37 (d, $J$ = 8.1 Hz, 2H), 7.24 (d, $J$ = 4.1 Hz, 1H), 7.05 (d, $J$ = 8.1 Hz, 2H), 6.77 (d, $J$ = 8.3 Hz, 2H), 6.55 (d, $J$ = 4.1 Hz, 1H), 6.53 (s, 1H), 6.46 (d, $J$ = 2.3 Hz, 2H), 6.38 (dd, $J$ = 8.3, 2.3 Hz, 2H), 6.05 (s, 1H), 3.83 (s, 3H), 3.78 (s, 9H), 3.71 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz) $\delta$ 160.2, 159.3, 158.3, 157.6, 142.7, 135.6, 131.4, 130.7, 129.0, 129.0, 127.8, 104.7, 103.7, 99.1, 98.9, 55.9, 55.7, 55.6, 55.4, 41.8. MALDI-TOF *m/z*, 500.935 $[M]^+$, 523.990 $[M + Na]^+$.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra, Ortep drawings for **1**, **2**, **4**, **5**, **6**, **9**, **13b**, **13e**, **18**, **19**, and **20**, and CIF files for **1**, **2**, **4**, **5**, **6**, **9**, **13b**, **13e**, **18**, **19**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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