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Electrocyclization-Mediated Approach to 2-Methyltriclisine, an Unnatural Analog of the Azafluoranthene Alkaloid Triclisine

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The synthesis of 2-methyltriclisine, an unnatural analog of the azafluoranthene alkaloid triclisine, is reported. The synthesis was achieved in 10 steps and 21 % overall yield from 2-bromo-3,4-dimethoxybenzaldehyde, through the intermediacy of 3,4-dimethoxyfluoren-9-one. Construction of the heterocyclic ring entailed the *para*-Claisen rearrangement of an allyl-4-fluorenyl ether, followed by isomerization of the resulting 2-allylfluoren-9-one and a microwave-assisted electrocyclization of the aza 6π-electron system formed by oximation of its carbonyl function.
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Introduction

The azafluoranthenes are ubiquitous in nature; the parent bases have been found in coal tar, cigarette smoke, river and lake sediments and also as air pollutants in street dust.[1] Being nitrogen-containing polycyclic aromatic compounds, these heterocycles are also considered among the environmental priority contaminants.[2]

The azafluoranthene alkaloids are a small and unique class of naturally occurring compounds containing the indeno[1,2,3-*ij*]isoquinoline motif (**1a**, Figure 1);[3] it includes the non-phenolic tetracycles rufescine (**1b**), imeluteine (**1c**) and triclisine (**1d**),[3b] isolated from the Amazonian vines *Abuta rufescens*, *A. imene* and *Triclisia gilletii* (Dewild) Staner (Menispermaceae), respectively.

In addition, norrufescine (**1e**), found in *A. rufescens*, *A. imene* and *Telitoxicum peruvianum*, together with telitoxine (**1f**), isolated from *T. peruvianum* and *T. glaziovii*[3c] and norimeluteine (**1g**) obtained from the tropical climbing shrub *Cissampelos pareira*,[3d] constitute the phenolic members of this family.

These compounds share some structural features with the naturally occurring 2,7-diazafluoranthenes like eupolauridine (**2a**) and its *N*-oxides **2b**, **2c** that can be found in Annonaceae, as well as with the less widespread stephaoxocanes, such as stephaoxocanidine (**3a**) and eletefine (**3b**) and the tropolo-isoquinolines, exemplified by grandirubrine (**4a**) and imerubrine (**4b**).[4] Compounds carrying the latter two skeletons have been isolated from Menispermaceous plants, including species which are also sources of azafluoranthene alkaloids.[5a] Furthermore, azafluoranthene derivatives have been prepared as part of some synthetic efforts toward tropolo-isoquinolines.[5b,5c]

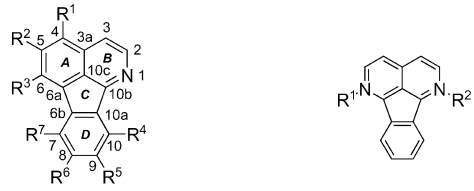

Figure 1. Chemical structures of indeno[1,2,3-*ij*]isoquinoline (**1a**), the azafluoranthene alkaloids **1b**–**g** and related natural products, including the eupolauridines **2a**–**c**, stephaoxocanes **3a**,**b** and tropolo-isoquinolines **4a**,**b**.

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The azafluoranthene alkaloids display various properties of biological and technological interest. They have been patented as constituents of wound-healing agents[6a] and have been reported to possess antidepressant activity.[6b] In addition, compounds **1e** and **1g** were isolated with the aid of a bioassay guided fractionation, monitoring the cytotoxicity against *P*-388 cells and demonstrated to be active at 5.8 μg/mL and 3.6 μg/mL, respectively,[3d] while related 4-azafluoranthene derivatives have been shown to act as 5-hydroxytryptamine subclass 3 receptor (5-HT_3) agonists.[6c]

Furthermore, as part of their efforts aimed to develop new approaches to discotic liquid crystals, which form tilted columnar phases with ferroelectric properties, Scherowsky et al. synthesized the azafluoranthene derivative **1h** and determined its crystal structure, confirming the suitability of the tetracycle for the formation of discotic phases.[7]

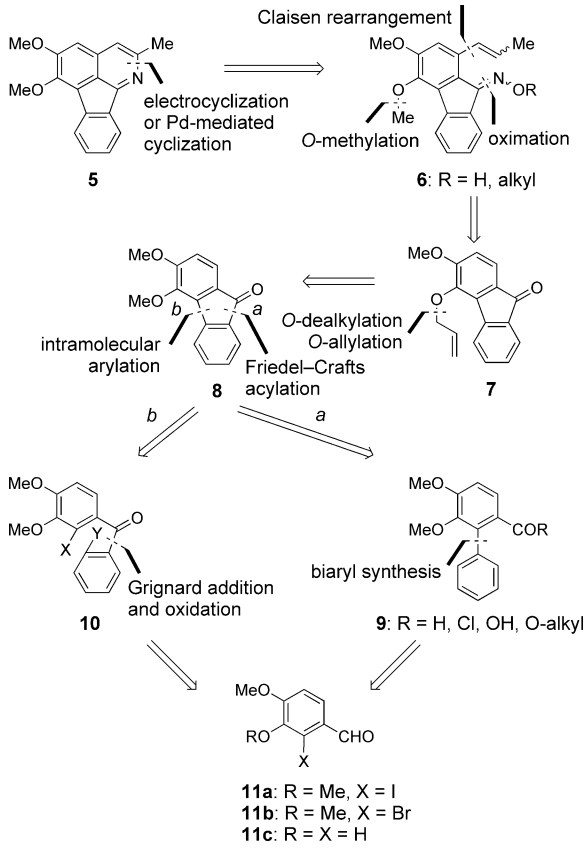
The main synthetic approach used toward azafluoranthenes has been the Pschorr-type cyclization of 1-(2-aminopheny1)-3,4-dihydro- and 1,2,3,4-tetrahydro-isoquinoline derivatives.[8] Other strategies have included the use of 8-phenylisoquinolin-1-one intermediates,[9a] the inverse electron demand Diels–Alder reaction of 3-methoxycarbonyl-2-pyrones[9b] and an aza-Wittig reaction in tandem with an intramolecular oxidative biaryl coupling under promotion of vanadium reagents,[9e] as well as metallation cross-coupling[9c] and photochemical[9d] reaction schemes. Interestingly, some unsuccessful attempts have also been disclosed.[10]

In pursuit of our interest in the elaboration of polycyclic tetrahydroisoquinoline-type natural products, their derivatives[11] and bioactive analogs,[12] herein we report the synthesis of 2-methyltriclisine (**5**), an unnatural analog of triclisine (**1d**), from the known 3,4-dimethoxyfluoren-9-one (**8**) and a new synthesis of this tricyclic ketone. The reaction sequence toward **5** features the electrocyclization reaction of an aza 6π-electron system as the final key transformation, which involves formation of the N–2C bond. Synthesis of isoquinoline derivatives based on the formation of this bond is still one of the less exploited strategic alternatives toward constructing these heterocyles; however, it is currently receiving considerable attention.[13]

Results and Discussion

As shown in the retrosynthetic analysis of **5** depicted in Scheme 1, we envisioned that our target could be obtained from oxime derivative **6**; in turn, it was considered that this intermediate would be accessed from fluoren-9-one **7**, through a sequence which should include the Claisen rearrangement of its allyl ether moiety, as well as *O*-methylation and oximation of the fluoren-9-one carbonyl. Finally, **7** could be reached from the known fluoren-9-one **8**.[14]

However, among the reported routes toward **8**, the most efficient one furnished the fluorenone in six steps and approximately 60% overall yield, from 2,3,4-trimethoxybenzoic acid.[14a] We concluded that this sequence was excessively long, partly because of the need of introducing and removing activating and protecting groups. Threrefore, and taking into account the technological and biomedical importance of fluoren-9-ones, their usefulness as synthetic intermediates and their occurrence as natural products,[15] we also decided to devise a new strategy toward **8**.



Scheme 1. Retrosynthetic analysis of 2-methyltriclisine (**5**).

Despite that a number of different approaches to fluoren-9-ones have been reported, the most useful ones belong to either one of two groups. The first one (route *a*) involves formation of the five-membered ring by closure of a properly functionalized biphenyl intermediate (**9**), usually through an intramolecular acylation, while the second and comparatively less explored group consists of the intramolecular arylation (route *b*) of a suitably activated benzophenone-type precursor (**10**).[16]

We conjectured that for our purpose, in either case known aldehydes **11a**,**b**[17a,17b] readily available in gram quantities from isovanillin (**11c**) through its selective *ortho*-halogenation, followed by a Williamson etherification of the free phenol, would be appropriate starting materials. The high atom efficiency of transition metal-mediated "direct" arylations inclined us toward exploring the intramolecular arylation alternative.

Therefore, the synthesis (Scheme 2) began with the treatment of iodoaldehyde **11a**[17a] with phenylmagnesium bromide. This furnished 85% of benzhydrol **12a**, which once oxidized with PDC, gave 93% of benzophenone derivative **10a**, setting the stage for the exploration of the direct palladium-catalyzed intramolecular biaryl coupling.[18]

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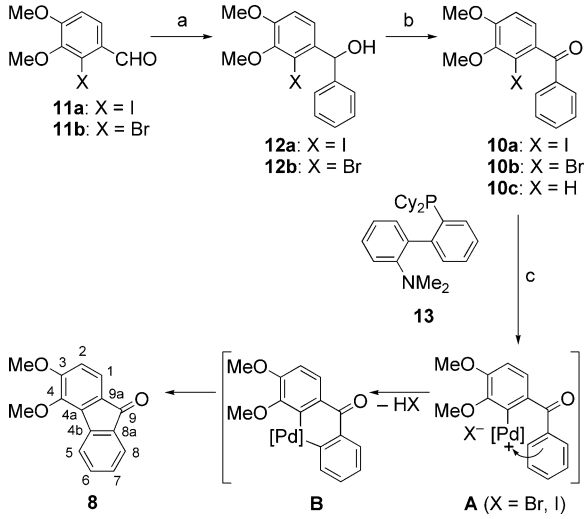


Scheme 2. Reagents and conditions: a) PhMgBr, THF, 0 °C→r.t. (**12a**, 85%; **12b**, 94%); b) PDC, CH_2Cl_2, room temp., 15 h (**10a**, 93%; **10b**, 92%); c) $Pd(PPh_3)_4$, DavePhos (**13**), KOAc, K_2CO_3, DMA, 110 °C, 22 h (**10a**→**8**, 34%; **10b**→**8**, 88–96%).

However, when cyclization of **10a** was attempted using the $Pd(OAc)_2$–triethanolamine reagent system,[19] the dehalogenated starting material (**10c**)[17c] was obtained as the sole product in 84% yield (Table 1). On the other hand, submission of **10a** to cyclization in dimethylacetamide (DMA) under $Pd(PPh_3)_4$ catalysis, employing DavePhos (**13**) as ligand in the presence of a mixture of KOAc and K_2CO_3, gave only 34% yield of **8**, along with 19% of the dehalogenated benzophenone **10c**, which hindered the purification of the cyclized product.

Taking into account that iodide salts have been found to exert a poisoning effect in the direct arylation reaction,[20a] the analogous bromoaldehyde **11b**[17b] was employed as starting material for a similar reaction sequence, furnishing benzophenone **10b** in 87% overall yield. To our satisfaction, after several attempts it was observed that submission of **10b** to the $Pd(PPh_3)_4$-catalyzed cyclization in DMA, employing ligand **13** in the presence of a mixture of KOAc and K_2CO_3, smoothly and consistently afforded **8**, in yields ranging from 88 to 96% after heating 22 h at 110 °C. Considerably reduced yields were observed, in the absence of K_2CO_3, while use of $Pd(OAc)_2$ as source of palladium resulted in complete decomposition of the starting material when triethanolamine was employed as solvent.

The cyclization reaction of aldehydes **10a**,**b** to furnish **8** probably proceeds through the initial oxidative addition of the palladium catalyst to the starting aryl halide to afford an arylpalladium halide intermediate (**A**), the Pd^{II} center of which would then undergo intramolecular nucleophilic attack by the phenyl moiety, yielding complex **B** after deprotonation, as first suggested by the group of Miura.[20b–20d]

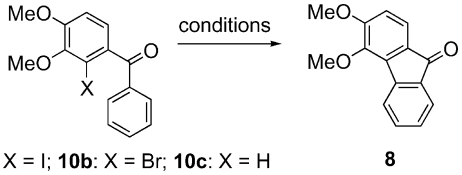
Then, reductive elimination of Pd^0 from complex **B** should result in formation of the required biaryl bond and release of the catalyst. Being an electron-rich ligand, the bulky Buchwald's phosphane **13** may facilitate both, the oxidative addition step and also dissociation of the halide, yielding a more reactive cationic palladium(II) species (**A**).

Having secured a short and efficient access of fluoren-9-one **8**, we turned our attention to the task of dealkylating its 4-OMe group. Sodium alkyl sulfides have gained general acceptance as efficient and selective agents for dealkylation of methyl ethers.[21] Not quite unexpectedly, when **8** was submitted to reaction with sodium ethyl sulfide in DMF, a 60:40 inseparable mixture of both possible mono-methyl ethers **14a** and **14b**, as assessed by ^1H NMR integration of the signals of their methyl ether moieties, was smoothly obtained in 92% combined yield (Scheme 3).

Interestingly, however, despite that the stabilizing effect on the phenoxide intermediate resulting from dealkylation of a methyl ether *ortho*/*para* to an electron-withdrawing group has been invoked as a factor that may facilitate a second *O*-demethylation process,[22a] in this case the bis-demethylated product could not be detected.

The observed product ratio is also interesting, given the apparent key role that electronic factors play in the selectivity of this process, which is particularly prone to dealkyate methyl ethers located *ortho* or *para* to electron-withdrawing groups.[22b] The preferred demethylation of the *ortho*-disubstituted methyl ether moiety[23a,23b] could arise from the out-of-plane preferred conformation adopted by the methyl group in these compounds, which may facilitate their reac-

Table 1. Optimization of the direct arylation reaction.



10a: X = I; **10b**: X = Br; **10c**: X = H — **8**

Starting material	Pd source	Reagents and conditions	Product (% yield)
10a	$Pd(OAc)_2$	$N(CH_2CH_2OH)_3$, microwave, 120 °C, 10 min	**10c** (84)
10a	$Pd(PPh_3)_4$	KOAc, K_2CO_3, **13**, DMA, 110 °C,[a] 23 h	**8** (34)
10b	$Pd(OAc)_2$	$N(CH_2CH_2OH)_3$, microwave, 120 °C, 30 min	deccomposition
10b	$Pd(PPh_3)_4$	KOAc, **13**, DMA, 135 °C,[a] 4 h	**8** (56)
10b	$Pd(PPh_3)_4$	KOAc, K_2CO_3, **13**, DMA, 110 °C,[a] 22 h	**8** (88–96)

[a] Bath preheated at the designated temperature.

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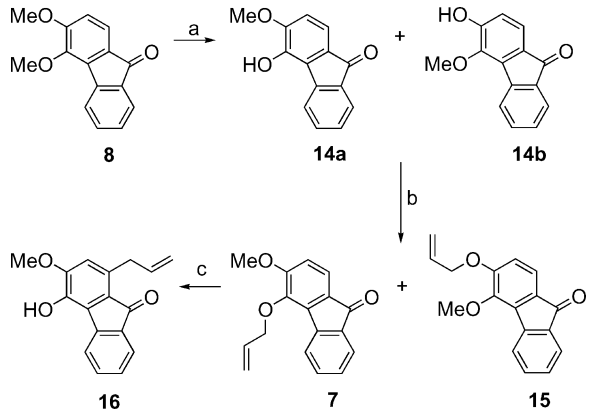
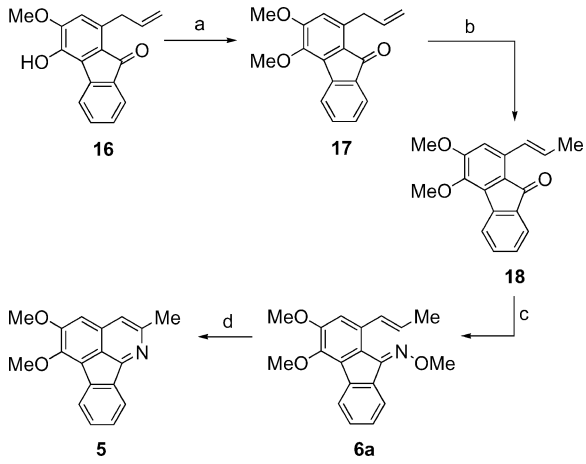


Scheme 3. Reagents and conditions: a) NaH, EtSH, DMF, 50 °C, 17 h (**14a/14b** = 60:40); b) $H_2C{=}CHCH_2Br$, K_2CO_3, EtOH, reflux, 90 min (**7**, 52%; **15**, 33%, from **8**); c) 1,2-Cl_2-C_6H_4, reflux, 12 h (80%).



Scheme 4. Reagents and conditions: a) MeI, K_2CO_3, EtOH, reflux, 2 h (92%); b) $PdCl_2(MeCN)_2$, CH_2Cl_2, reflux, 60 h (90%); c) $H_2NOMe{\cdot}HCl$, NaOAc, EtOH, 2 h (95%); d) 1,2-Cl_2-C_6H_4, microwave (115 W, 180 °C), 60 min (81%).

tion with the sulfur nucleophile. Unfortunately, use of the more hindered sodium *tert*-butyl sulfide did not provide better selectivity, furnishing at best a 1.07:1 ratio of monomethyl derivatives, in 68% combined yield after conducting the reaction 10 h at 50 °C.

Without further purification, the mixture of phenols **14a**,**b** was treated with allyl bromide and anhydrous potassium carbonate in absolute EtOH, yielding **7** and **15** in 52% and 33% overall yield, respectively, after chromatographic separation. Unequivocal identification of both pair of compounds, the phenols **14a**,**b** and their corresponding allyl ethers **7** and **15** was aided by the clearly evident 4–5 ppm downfield shift of the methyl carbon atom in the fluoren-9-ones **14b** and **15**, which bear an *ortho* disubstituted methyl ether.[23b,23c]

Next, the projected *para*-Claisen rearrangement of **7** was performed. Despite that microwave heating of the allyl ether in 1,2-Cl_2-C_6H_4 (180 °C, 2 h) and in Ph_2O (180 °C, 80 min or 260 °C, 20 min) furnished rearranged products in acceptable yields, the best results were achieved by submitting the allyl ether to conventional reflux in 1,2-Cl_2-C_6H_4. This gave allylfluorenone derivative **16** in 80% yield. The product, which displayed 2-H as a singlet in its ^{1}H NMR spectrum (δ_H = 6.46 ppm), was uneventfully alkylated under standard conditions (Scheme 4), with MeI in refluxing EtOH to which excess K_2CO_3 was added, giving 1-allylfluoren-9-one **17** in 92% yield.

In order to elaborate the heterocyclic ring, two alternatives were considered. One of them included the established thermal electrocyclization of an *ortho*-propenyl oxime,[24] while the second possibility consisted in the palladium-catalyzed cyclization of an oxime derived from the the 1-allylfluorenone derivative **17**, as described by Tsutsui and Narasaka.[25] The latter transformation does not seem to imply isomerization of the allyl moiety and electrocyclization of the resulting intermediate; however, since its reported yields were only moderate, the first alternative was pursued.

Therefore, the allyl moiety of **17** was first isomerized with $PdCl_2(MeCN)_2$ in refluxing CH_2Cl_2 during 60 h[26] to give 90% of the 1-propenyl-fluorenone derivative **18** as a single isomer to which the *E* configuration was attributed, on the basis of the observed coupling constants between its vinylic protons (J = 15.9 Hz).

Secondly, **18** was subjected to oximation with methoxylamine hydrochloride, furnishing 89% of the corresponding *N*-methoxy oxime **6a**. Interestingly, again only one isomer was detected, to which the *anti* stereochemistry was assigned on the basis that this configuration avoids the steric congestion between the vinylic protons of the propenyl group and the methoxy moiety of the oxime.

Finally, submission of the 1-azatriene **6a** to the proposed microwave-assisted electrocyclization reaction, smoothly furnished the expected final product **5**. The best results were obtained when the transformation was carried out in 1,2-Cl_2-C_6H_4, where 81% yield of product was obtained, after heating at 180 °C during 1 h.

A detailed spectroscopic analysis of **5** was carried out, based on evidences provided by HMQC, HMBC and selective NOE experiments, which allowed the unequivocal assignment of its ^{1}H and ^{13}C NMR resonances.

The observation of signal enhancement of 7-H upon irradiation of the 6-OMe group in the NOE experiment, unambiguously located the chemical shift of 7-H; this also allowed to establish that 5-OMe (δ_H = 3.97 ppm) is more shielded than 6-OMe (δ_H = 4.04 ppm), suggesting that the previously reported assignments for these groups in triclisine (**1d**)[27] could be reversed.

Conclusions

The synthesis of 2-methyltriclisine (**5**), an unnatural analog of the azafluoranthene alkaloid triclisine (**1d**) was achieved, in ten steps and 21% overall yield from 2-bromo-3,4-dimethoxy benzaldehyde (**11a**), through the intermediacy of known 3,4-dimethoxyfluoren-9-one (**8**) and without

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resorting to the use of protecting groups. The synthesis features a *para*-Claisen rearrangement and a microwave assisted 6π electrocyclization reaction of a properly substituted 1-propenylfluoren-9-one-oxime for construction of the heterocyclic ring. In addition, it includes a new and efficient three-step synthesis of **8**, in 78% overall yield from 2-bromo-3,4-dimethoxybenzaldehyde (**11a**), employing a strategy consisting in Grignard addition to polysubstituted benzaldehyde **11a**, followed by oxidation of the so produced benhydrol and a palladium-catalyzed direct arylation of the resulting benzophenone, as key transformation.

Experimental Section

General: The reactions were carried out under dry nitrogen or argon atmosphere, employing oven-dried glassware. Reagents were used as received; anhydrous THF was prepared by distillation from Na-benzophenone ketyl; anhydrous DMF was obtained by heating the PA grade product over BaO for 4 h, followed by distillation under reduced pressure; absolute EtOH was accessed by refluxing the solvent over clean magnesium turnings and distilling from the resulting magnesium ethoxide; anhydrous DMA and 1,2-dichlorobenzene were prepared by distillation of the corresponding commercial products; anhydrous CH_2Cl_2 was prepared by a 4 h reflux of the solvent over P_2O_5 followed by distillation; anhydrous solvents were stored in dry Young ampoules. All other reagents were used as received.

In the conventional work-up procedure, the reaction mixture was diluted with brine (5–10 mL) and the products were extracted with EtOAc (4–5 × 20 mL); the combined organic extracts were then washed once with brine (5 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography with silica gel 60 H. Elution was carried out with hexane/EtOAc mixtures, under positive pressure and employing gradient of solvent polarity techniques. All new compounds gave single spots on TLC plates run in different hexane/EtOAc and CH_2Cl_2/toluene solvent systems. Chromatographic spots were detected by exposure to 254 nm UV light, followed by spraying with ethanolic ninhydrin (nitrogen-containing compounds) or with ethanolic *p*-anisaldehyde/sulfuric acid reagent and careful heating of the plates for improving selectivity.

Melting points were determined on an Leitz hot-stage microscope (model 350) and are reported uncorrected. FTIR spectra were acquired with a Shimadzu Prestige 21 spectrophotometer as thin films held between NaCl cells or as solid dispersions in KBr disks. The ^1H and ^{13}C NMR spectra were acquired in $CDCl_3$ in a Bruker Avance spectrometer (300.13 and 75.48 MHz for ^1H and ^{13}C, respectively). The chemical shifts are reported in parts per million downfield from tetramethylsilane used as internal standard, and coupling constants (*J*) are expressed in Hertz. DEPT 135 and DEPT 90 experiments aided the interpretation and assignment of the fully decoupled ^{13}C NMR spectra. In special cases, 2D-NMR experiments (COSY, HMBC and HMQC) were also employed. Pairs of signals marked with asterisks (*) or hashes (#) indicate that their assignments may be exchanged. GC-MS analyses were performed with a Perkin–Elmer Q-700 spectrometer equipped with an apolar fused silica capillary column (30 m × 0.25 mm), coated with 5% phenyl- and 95% dimethyl-polysiloxane (DB-5, coating thickness 0.25 μm). High-resolution mass spectroscopic data were obtained from the University of California, Riverside (USA). Formation of fluoren-9-one **8** was monitored employing a Shimadzu model 14B gas chromatograph fitted with a J&W Scientific 30 m × 0.25 mm polydimetylsiloxane capillary column and a flame ionization detector. Hydrogen (1 mL/min) was employed as carrier gas. Chromatographic parameters were: T_{det} = 270 °C; T_{inj} = 250 °C. The temperature gradient program was 50–250 °C at 10 °C/min. Microwave-assisted reactions were performed in a CEM Discover microwave oven.

3,4-Dimethoxyfluoren-9-one (8) from 2-Iodo-3,4-dimethoxybenzaldehyde (11a): A stirred solution of aldehyde **11a** (400 mg, 1.37 mmol) in THF (15 mL) was cooled to –40 °C and treated dropwise (20 min) with a freshly prepared THF solution of phenylmagnesium bromide (0.30 M, 6 mL). After 1 h, the reaction was treated with saturated NH_4Cl solution (5 mL), the system was allowed to reach room temperature and the product was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (10 mL), dried with Na_2SO_4 and subjected to chromatography, giving (2-iodo-3,4-dimethoxyphenyl)phenylmethanol (**12a**) (594 mg, 85%), as a white solid; m.p. 123–125 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 3469, 2961 1950, 1584, 1476, 1393, 1278, 1134, 1026, 916, 814, 729 (and 661) cm^{-1}. ^1H NMR: δ = 2.51 (br. s, 1 H, $w_{1/2}$ = 7.2 Hz, OH), 3.83 (s, 3 H, 3-OMe), 3.86 (s, 3 H, 4-OMe), 6.10 (s, 1 H, ArC*H*), 6.88 (d, *J* = 8.6 Hz, 1 H, 5-H), 7.15 (d, *J* = 8.6 Hz, 1 H, 6-H), 7.25–7.42 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 56.1 (4-OMe), 60.3 (3-OMe), 78.7 (C-OH), 98.2 (2-C), 112.5 (5-C), 124.1 (6-C), 127.1 (2 C, 2-C′ and 6-C′), 127.6 (4-C′), 128.4 (2 C, 3-C′ and 5-C′), 138.6 (1-C), 142.6 (1-C′), 148.5 (3-C), 152.0 (4-C) ppm. GC/MS: *m*/*z* (%) = 370 (88) [M^+], 293 (21), 211 (30), 165 (39), 105 (100). Without further purification, a stirred solution of **12a** (406 mg, 1.10 mmol) in anhydrous CH_2Cl_2 (25 mL) was treated with PDC (515 mg, 1.37 mmol) at room temperature. The resulting suspension was stirred until complete consumption of the starting material (15 h); then, the slurry was filtered through Celite and concentrated under reduced pressure to give an oily residue, which was chromatographed, affording (2-bromo-3,4-dimethoxyphenyl)phenylmethanone **10a** (375 mg, 93%), as a yellowish solid; m.p. 117–119 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 2938, 2840, 1668, 1577, 1476, 1386, 1274, 1155, 1024, 959, 851, 717, 627 cm^{-1}. ^1H NMR: δ = 3.87 (s, 3 H, 3-OMe), 3.93 (s, 3 H, 4-OMe), 6.95 (d, *J* = 8.4 Hz, 1 H, 5-H), 7.06 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.44 (br. dd, *J* = 7.4, 7.9 Hz, 2 H, 3′-H and 5′-H), 7.59 (dt, *J* = 1.2, 7.4 Hz, 1 H, 4′-H), 7.80 (dd, *J* = 1.2, 7.9 Hz, 2 H, 2′-H and 6′-H) ppm. ^{13}C NMR: δ = 56.1 (4-OMe), 60.5 (3-OMe), 92.2 (2-C), 111.8 (5-C), 125.3 (6-C), 128.5 (2 C, 3-C′ and 5-C′), 130.5 (2 C, 2-C′ and 6-C′), 133.4 (4-C′), 136.3 (1-C′), 137.3 (1-C), 149.2 (3-C), 155.0 (4-C), 196.6 (C=O) ppm. Anhydrous KOAc (19 mg, 0.19 mmol), DavePhos (3.7 mg, 0.0095 mmol) and K_2CO_3 (26 mg, 0.19 mmol) were succesively added to a solution of $Pd(PPh_3)_4$ (6.5 mg, 0.0057 mmol) in DMA (1.5 mL) and the resulting suspension was stirred at room temperature during 15 min, when a solution of iodobenzophenone **10a** (35 mg, 0.095 mmol) in DMA (0.5 mL) was introduced via a cannula. The system was heated at 110 °C until all the starting material was consumed (23 h). Then, the solvent was removed in vacuo at 35 °C and the remaining solid was suspended in EtOAc (4 mL), filtered through a short plug of cotton and transferred to a separatory funnel. Water (4 mL) was added to remove dissolved salts and the aqueous phase was back-extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine (2.5 mL), dried with $MgSO_4$ and chromatographed, furnishing the benzophenone derivative **10c** (4.3 mg, 19%) as a white solid; m.p. 88–90 °C (hexane/EtOAc; ref.[17c] 86–90 °C). IR (KBr): $\tilde{\nu}$ = 3000, 2940, 2840, 1660, 1580, 1480, 1320, 1250, 1180, 1030, 964, 814, 770, 690 cm^{-1}. ^1H NMR: δ = 3.94 (s, 3 H, OMe),

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3.96 (s, 3 H, OMe), 6.89 (d, J = 8.4 Hz, 1 H, 5-H), 7.38 (dd, J = 1.8, 8.4 Hz, 1 H, 6-H), 7.44–7.52 (m, 2 H, 3′-H and 5′-H), 7.50 (d, J = 1.8 Hz, 1 H, 2-H), 7.57 (ddt, J = 1.4, 6.6, 8.3 Hz, 1 H, 4′H), 7.76 (dd, J = 1.4, 8.3 Hz, 2 H, 2′-H and 6′-H) ppm. ^{13}C NMR: δ = 56.0 (OMe), 56.1 (OMe), 109.7 (5-C), 112.1 (2-C), 125.5 (6-C), 128.2 (2 C, 3′-C and 5′-C), 129.7 (2 C, 2′-C and 6′-C), 130.2 (1-C), 131.9 (4′-C), 138.3 (1′-C), 149.0 (3-C), 153.0 (4-C), 195.6 (C=O) ppm. Increasing solvent polarity provided fluoren-9-one **8** (11.3 mg, 34%), as a bright yellow solid; m.p. 143.5–145 °C (hexane/EtOAc, ref.[14] 143–144.5 °C). IR (KBr): $\tilde{\nu}$ = 2924, 2831, 1702, 1610, 1599, 1494, 1256, 1104, 1021, 959, 818, 756, 606 cm^{-1}. ^{1}H NMR: δ = 3.93 (s, 3 H, 3-OMe), 3.96 (s, 3 H, 4-OMe), 6.73 (d, J = 8.0 Hz, 1 H, 2-H), 7.26 (t, J = 7.4 Hz, 1 H, 7-H), 7.41 (d, J = 8.0 Hz, 1 H, 1-H), 7.46 (t, J = 7.4 Hz, 1 H, 6-H), 7.62 (d, J = 7.4 Hz, 1 H, 8-H), 7.83 (d, J = 7.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 56.2 (3-OMe), 60.4 (4-OMe), 111.2 (2-C), 121.4 (1-C), 123.8 (8-C), 124.0 (5-C), 128.0 (9a-C), 128.8 (7-C), 134.5 (6-C), 135.2 (8a-C), 136.3 (4a-C), 142.5 (4b-C), 144.8 (4-C), 159.1 (3-C), 192.4 (C=O) ppm. GC/MS: m/z (%) = 368 (100) [M$^+$], 291 (98), 226 (34), 105 (68).

(2-Bromo-3,4-dimethoxyphenyl)phenylmethanol (12b): A stirred solution of 2-bromo-3,4-dimethoxybenzaldehyde (**11b**, 500 mg, 2.04 mmol) in THF (8 mL) was cooled to 0 °C and treated dropwise (20 min) with a freshly prepared THF solution of phenylmagnesium bromide (0.34 M, 7.3 mL). After 1.5 h, the reaction was warmed to room temperature, saturated NH_4Cl solution (10 mL) was added and the product was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (2 × 10 mL), dried with $MgSO_4$ and subjected to chromatography, furnishing **12b** (617 mg, 94%), as a white solid; m.p. 102–103 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 3500, 2936, 2836, 1593, 1485, 1280, 1142, 1031, 921, 812, 728, 649 cm^{-1}. ^{1}H NMR: δ = 2.80 (br. s, 1 H, $w_{1/2}$ = 15 Hz, OH), 3.84 (s, 3 H, 3-OMe), 3.85 (s, 3 H, 4-OMe), 6.16 (s, 1 H, ArC*H*), 6.87 (d, J = 8.8 Hz, 1 H, 5-H), 7.20 (d, J = 8.8 Hz, 1 H, 6-H), 7.26–7.38 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 56.1 (4-OMe), 60.5 (3-OMe), 74.6 (C-OH), 111.4 (5-C), 118.9 (2-C), 123.6 (6-C), 126.9 (2 C, 2-C′ and 6-C′), 127.6 (4-C′), 128.3 (2 C, 3-C′ and 5-C′), 135.7 (1-C), 142.5 (1-C′), 146.2 (3-C), 152.9 (4-C) ppm. HRMS calcd. $C_{15}H_{14}BrO_3$: 321.0121 [M$^+$ – H]; found 321.0121.

(2-Bromo-3,4-dimethoxyphenyl)phenylmethanone (10b): A solution of **11b** (420 mg, 1.30 mmol) in anhydrous CH_2Cl_2 (13.4 mL) was treated with PDC (1.285 g) at room temperature. The resulting suspension was stirred until full consumption of the starting material (20 h); then, it was filtered through Celite and concentrated to give an oily residue, which was chromatographed to afford benzophenone **10b** (382 mg, 92%) as a white solid; m.p. 121–122 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 3002, 2937, 2839, 1658, 1587, 1486, 1321, 1299, 1180, 1034, 964, 813, 720, 699 cm^{-1}. ^{1}H NMR: δ = 3.89 (s, 3 H, 3-OMe), 3.93 (s, 3 H, 4-OMe), 6.87 (d, J = 8.8 Hz, 1 H, 5-H), 7.21 (d, J = 8.8 Hz, 1 H, 6-H) 7.45 (br. dd, J = 7.9, 7.4 Hz, 2 H, 3′-H and 5′-H), 7.58 (dt, J = 1.2, 7.4 Hz, 1 H, 4′-H), 7.80 (dd, J = 1.2, 7.9 Hz, 2 H, 2′-H and 6′-H) ppm. ^{13}C NMR: δ = 56.2 (4-OMe), 60.7 (3-OMe), 110.9 (5-C), 116.2 (2-C), 125.1 (6-C), 128.5 (2 C, 3-C′ and 5-C′), 130.2 (2 C, 2-C′ and 6-C′), 133.4 (4-C′), 133.7 (1-C), 136.7 (1-C′), 146.8 (3-C), 155.0 (4-C), 195.3 (C=O) ppm. HRMS calcd. $C_{15}H_{14}BrO_3$: 321.0121 [MH$^+$]; found 321.0131.

3,4-Dimethoxyfluoren-9-one (8) from 2-Bromobenzophenone (10b): A solution of $Pd(PPh_3)_4$ (78 mg, 0.0675 mmol), in DMA (5 mL) was successivelly treated with anhydrous KOAc (219 mg, 2.23 mmol), DavePhos (44 mg, 0.111 mmol) and K_2CO_3 (309 mg, 2.24 mmol) and the resulting suspension was stirred at room temperature during 15 min, when a solution of benzophenone **10b** (350 mg, 1.09 mmol) in DMA (0.5 mL) was introduced via a cannula. The system was heated at 110–120 °C during 22 h, until all the starting material was consumed. Then, the solvent was removed in vacuo at 35 °C and the remaining solid was suspended in EtOAc (40 mL), filtered through a short plug of cotton and transferred to a separatory funnel. Water (40 mL) was added to remove dissolved salts and the aqueous phase was back-extracted with EtOAc (2 × 25 mL). The combined organic phases were washed with brine (25 mL), dried with $MgSO_4$ and chromatographed to furnish the fluoren-9-one derivative **8** (262 mg, 90%), the melting point and spectroscopic data of which were in agreement with those obtained for **8** when synthesized from iodooaldehyde **12a** through the intermediacy of 2-iodobenzophenone derivative **10a**.

4-Allyloxy-3-methoxyfluoren-9-one (7), and 3-Allyloxy-4-methoxyfluoren-9-one (15): A stirred solution of EtSH (0.27 mL, 3.6 mmol) in DMF (5.0 mL) was treated with a 50% dispersion of NaH in mineral oil (156.4 mg, 3.26 mmol) and heated at 50 °C during 20 min, when a solution of fluoren-9-one **8** (263 mg, 1.09 mmol) in DMF (1.5 mL) was added via cannula to the thus formed sodium ethanothiolate. The resulting reddish solution was stirred at 50 °C during 17 h, until complete consumption of starting ketone was verified by TLC. Then, the reaction was cautiously treated with 1.0 N HCl (15 mL), rendering a yellow solution, which was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (2 × 10 mL), dried with Na_2SO_4, concentrated under reduced pressure and chromatographed, yielding **14a** and **14b**, as an approximately 60:40 (by ^{1}H NMR:) inseparable mixture of regioisomers. Spectral data of **14a** ^{1}H NMR: δ = 3.92 (s, 3 H, 3-OMe), 6.15 (br. s, 1 H, $w_{1/2}$ = 6 Hz, OH), 6.64 (d, J = 8.0 Hz, 1 H, 3-H), 7.23 (t, J = 7.4 Hz, 1 H, 7-H), 7.39 (d, J = 8.0 Hz, 1 H, 2-H), 7.45 (t, J = 7.4 Hz, 1 H, 6-H), 7.61 (d, J = 7.4 Hz, 1 H, 8-H), 7.80 (d, J = 7.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 56.4 (3-OMe), 109.3 (2-C), 117.7 (1-C), 123.8 (5-C), 124.2 (8-C), 127.9 (9a-C), 128.1 (7-C), 129.0 (4a-C), 134.6 (6-C), 134.7 (8a-C), 136.7 (4b-C), 141.4 (4-C), 152.8 (3-C), 193.3 (C=O) ppm. Spectral data of **14b** ^{1}H NMR: δ = 3.96 (s, 3 H, 4-OMe), 6.83 (d, J = 8.0 Hz, 1 H, 3-H), 6.96 (br. s, 1 H, $w_{1/2}$ = 12 Hz, OH), 7.27 (d, J = 8.0 Hz, 1 H, 2-H), 7.25 (t, J = 7.4 Hz, 1 H, 7-H), 7.47 (t, J = 7.4 Hz, 1 H, 6-H), 7.63 (d, J = 7.4 Hz, 1 H, 8-H), 7.69 (d, J = 7.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 61.1 (4-OMe), 115.7 (2-C), 122.4 (3-C), 123.5 (5-C), 124.0 (8-C), 128.1 (9a-C), 128.3 (7-C), 134.6 (4a-C), 134.5 (6-C), 135.1 (8a-C), 141.7 (4b-C), 142.8 (4-C), 156.1 (3-C), 192.4 (C=O) ppm. The mixture of phenols (194.0 mg, 0.857 mmol) was dissolved in absolute EtOH (1.5 mL); allyl bromide (0.096 mL, 1.12 mmol) and K_2CO_3 (165.5 mg, 1.2 mmol) were added under gently stirring, and the resulting reddish suspension was heated under reflux for 1.5 h. Then, the suspension was filtered, the solids were washed with EtOAc (1 mL) and the filtrate was concentrated under reduced pressure, leaving a solid residue, which was chromatographed to afford allyl ether **15** (75 mg, 33% overall yield), as an oil. IR (KBr): $\tilde{\nu}$ = 3020, 2950, 2848, 1699, 1557, 1498, 1360, 1254, 1107, 1013, 926, 825, 758, 695 cm^{-1}. ^{1}H NMR: δ = 3.99 (s, 3 H, 4-OMe), 4.66 (dd, J = 1.4, 3.8 Hz, 2 H, ArOCH_2), 5.35 (dd, J = 1.4, 10.5 Hz, 1 H, CH=CH_{2cis}), 5.47 (dd, J = 1.4, 17.2 Hz, 1 H, CH=CH_{2trans}), 6.08 (dddd, J = 3.8, 3.8, 10.5, 17.2 Hz, 1 H, C*H*=CH$_2$), 6.73 (d, J = 8.2 Hz, 1 H, 2-H), 7.26 (dt, J = 1.0, 7.5 Hz, 1 H, 7-H), 7.40 (d, J = 8.2 Hz, 1 H, 1-H), 7.47 (dt, J = 1.0, 7.5 Hz, 1 H, 6-H), 7.63 (dd, J = 1.0, 7.5 Hz, 1 H, 8-H), 7.85 (dd, J = 1.0, 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 60.4 (4-OMe), 69.7 (ArOCH$_2$), 112.6 (2-C), 118.3 (CH=*C*H$_2$), 121.2 (1-C), 123.8 (8-C), 124.0 (5-C), 128.2 (9a-C), 128.7 (6-C), 132.3 (*C*H=CH$_2$), 134.6 (7-C), 135.1 (8a-C), 136.5 (4a-C), 142.6 (4b-C), 145.0 (4-C), 158.0 (3-C), 192.5 (C=O) ppm. HRMS calcd. $C_{17}H_{15}O_3$: 267.1016 [MH$^+$];

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found 267.1017. Increasing solvent polarity allowed the isolation of desired regioisomer **7** (119 mg, 52% overall yield), as a yellowish solid; m.p. 78–79 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 3022, 2951, 2847, 1699, 1560, 1497, 1365, 1253, 1105, 1009, 926, 822, 757, 692 cm^{-1}. ^1H NMR: δ = 3.93 (s, 3 H, 3-OMe), 4.65 (br. d, J = 5.9 Hz, 2 H, ArOCH_2), 5.28 (dd, J = 1.4, 10.4 Hz, 1 H, CH=CH_{2cis}), 5.42 (dd, J = 1.4, 17.2 Hz, 1 H, CH=CH_{2trans}), 6.14 (dddd, J = 5.9, 5.9, 10.4, 17.2 Hz, 1 H, CH=CH_2), 6.74 (d, J = 8.0 Hz, 1 H, 2-H), 7.27 (t, J = 7.5 Hz, 1 H, 7-H), 7.43 (d, J = 8.0 Hz, 1 H, 1-H), 7.45 (t, J = 7.5 Hz, 1 H, 6-H), 7.63 (d, J = 7.5 Hz, 1 H, 8-H), 7.88 (d, J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 56.2 (3-OMe), 73.7 (Ar-OCH_2), 111.2 (2-C), 118.3 (CH=CH_2), 121.4 (1-C), 123.8 (8-C), 124.2 (5-C), 128.1 (9a-C), 128.7 (6-C), 133.8 (CH=CH_2), 134.5 (7-C), 135.2 (8a-C), 136.7 (4a-C), 142.6 (4b-C), 143.3 (4-C), 159.1 (3-C), 192.5 (C=O) ppm. HRMS calcd. $C_{17}H_{15}O_3$: 267.1016 [MH^+]; found 267.1018.

1-Allyl-4-hydroxy-3-methoxyfluoren-9-one (16): A solution of allyl ether **7** (93.0 mg, 0.349 mmol) in 1,2-Cl_2-C_6H_4 (3.0 mL) was heated at reflux, until complete consumption of the starting material was observed by TLC (12 h). Then, the solution was chromatographed yielding **16** (74 mg, 80%), as a bright yellow solid; m.p. 185–185.5 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 3411, 3069, 2937, 2850, 1625, 1599, 1466, 1385, 1249, 1129, 1004, 906, 851, 740, 666 cm^{-1}. ^1H NMR: δ = 3.80 (dd, J = 1.3, 5.3 Hz, 2 H, ArCH_2), 3.94 (s, 3 H, 3-OMe), 5.06 (ddd, J = 1.4, 3.0, 10.0 Hz, 1 H, CH=CH_{2cis}), 5.13 (ddd, J = 1.4, 3.0, 17.1 Hz, 1 H, CH=CH_{2trans}), 5.92 (s, 1 H, OH), 5.98 (dddd, J = 5.3, 5.3, 10.0, 17.1 Hz, 1 H, CH=CH_2), 6.46 (s, 1 H, 2-H), 7.23 (dt, J = 0.8, 7.5 Hz, 1 H, 7-H), 7.45 (dt, J = 1.1, 7.5 Hz, 1 H, 6-H), 7.60 (br. d, J = 7.5 Hz, 1 H, 8-H), 7.83 (br. d, J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 34.9 (ArCH_2), 56.4 (3-OMe), 110.9 (2-C), 116.0 (CH=CH_2), 123.4 (8-C), 124.0 (5-C), 124.4 (1-C), 128.0 (7-C), 128.5 (9a-C), 134.2 (6-C), 134.9 (8a-C),# 135.1 (4a-C),# 136.5 (CH=CH_2), 140.0 (4b-C),# 142.2 (4-C),# 152.3 (3-C), 193.6 (C=O) ppm. HRMS calcd. $C_{17}H_{15}O_3$: 267.1016 [MH^+]; found 267.1017.

1-Allyl-3,4-dimethoxyfluoren-9-one (17): MeI (0.090 mL, 1.45 mmol) and K_2CO_3 (34.8 mg, 0.362 mmol) were successively added to a stirred solution of allylphenol **16a** (64.3 mg, 0.242 mmol) in absolute EtOH (4.0 mL) and the resulting suspension was heated under reflux until complete consumption of the starting material was observed (2 h). The solvent was removed under reduced pressure, the remaining solid was diluted with brine (5 mL) and extracted with $CHCl_3$ (5 × 3 mL); filtration through a short pad of silica gave **17** (62 mg, 92%), as a yellow solid; m.p. 112.5–113.5 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 3066, 2972, 2829, 1697, 1505, 1425, 1371, 1257, 1172, 1023, 923, 836, 750, 665 cm^{-1}. ^1H NMR: δ = 3.83 (dt, J = 1.4, 6.9 Hz, 2 H, ArCH_2), 3.93 (s, 3 H, 3-OMe), 3.94 (s, 3 H, 4-OMe), 5.09 (ddd, J = 1.4, 3.0, 7.1 Hz, 1 H, CH=CH_{2trans}), 5.15 (ddd, J = 1.4, 3.0, 17.1 Hz, 1 H, CH=CH_{2cis}), 5.99 (dddd, J = 6.9, 6.9, 7.1, 17.1 Hz, 1 H, CH=CH_2), 6.53 (s, 1 H, 2-H), 7.26 (dt, J = 1.1, 7.5 Hz, 1 H, 7-H), 7.46 (dt, J = 1.1, 7.5 Hz, 1 H, 6-H), 7.60 (br. d, J = 7.5 Hz, 1 H, 8-H), 7.85 (br. d, J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 35.1 (ArCH_2), 56.1 (3-OMe), 60.4 (4-OMe), 112.7 (2-C), 116.3 (CH=CH_2), 123.5 (8-C), 123.8 (5-C), 124.1 (1-C), 128.7 (7-C), 134.3 (9a-C), 135.5 (8a-C), 136.2 (6-C), 136.7 (4a-C),# 138.9 (CH=CH_2), 141.9 (4b-C),# 143.4 (4-C),# 158.6 (3-C), 193.1 (C=O) ppm. HRMS calcd. $C_{18}H_{16}O_3$: 281.1172 [MH^+]; found 281.1173.

(*E*)-1-Propenyl-3,4-dimethoxyfluoren-9-one (18): A stirred solution of **17** (58.4 mg, 0.208 mmol) in CH_2Cl_2 (5.0 mL) was treated with $PdCl_2(MeCN)_2$ (4.7 mg, 0.018 mmol) and the reaction was refluxed during 60 h. The resulting black slurry was filtered through a short pad of Celite, and the filtrate was concentrated and chromatographed, furnishing the isomerized olefin **18** (53 mg, 90%), as a yellow solid; m.p. 174.5–175 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 2972, 2850, 1697, 1584, 1426, 1371, 1257, 1172, 1023, 924, 837, 750, 687 cm^{-1}. ^1H NMR: δ = 1.96 (dd, J = 1.7 and 6.8 Hz, 3 H, CH_2-*Me*), 3.93 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 6.37 (dq, J = 6.8, 15.9 Hz, 1 H, CH-Me), 6.83 (s, 1 H, 2-H), 7.26 (dt, J = 1.4, 7.5 Hz, 1 H, 7-H), 7.45 (dt, J = 1.4, 7.5 Hz, 1 H, 6-H), 7.61 (dd, J = 1.4, 7.5 Hz, 1 H, 8-H), 7.63 (dd, J = 1.7, 15.9 Hz, 1 H, ArCH=CH), 7.85 (dd, J = 1.4, 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 18.8 (CH-*Me*), 56.0 (3-OMe), 60.4 (4-OMe), 107.0 (2-C), 122.5 (1-C), 123.4 (8-C), 123.7 (5-C), 126.1 (Ar*C*H=CH), 128.6 (7-C), 129.9 (ArCH=CH), 134.1 (6-C), 135.6 (9a-C),* 135.8 (8a-C),* 136.0 (4a-C),# 141.8 (4b-C),# 143.9 (4-C),# 158.4 (3-C), 193.2 (C=O) ppm. HRMS calcd. $C_{18}H_{17}O_3$: 281.1172 [MH^+]; found 281.1171.

(*E*)-1-Propenyl-3,4-dimethoxyfluoren-9-one (*Z*)-*O*-Methyl Oxime (6a): *O*-Methyl hydroxylamine hydrochloride (177.4 mg, 2.12 mmol) and anhydrous NaAcO (174.2 mg, 2.12 mmol) were successively added to a stirred solution of **18** (25.3 mg, 0.0903 mmol) in absolute EtOH (3.0 mL), and the reaction was refluxed overnight, when an additional amount of methoxyamine hydrochloride (50 mg) was added in order to drive the process to completion. Then, the greenish suspension was evaporated to dryness and the residue was subjected to column chromatography, furnishing *N*-methoxy oxime **6a** (22 mg, 89%), as a pale yellow solid; m.p. 87–88 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 3048, 2931, 2828, 1603, 1567, 1428, 1372, 1293, 1198, 1057, 843, 740, 697 cm^{-1}. ^1H NMR: δ = 1.97 (dd, J = 1.8, 6.6 Hz, 3 H, CH-*Me*), 3.94 (s, 3 H, 3-OMe), 3.96 (s, 3 H, 4-OMe), 4.22 (s, 3 H, *N*-OMe), 6.28 (dq, J = 6.6, 15.8 Hz, CH=Me), 6.94 (s, 1 H, 2-H), 7.29 (dt, J = 1.0, 7.6 Hz, 1 H, 6-H), 7.41 (dt, J = 1.0, 7.6 Hz, 1 H, 7-H), 7.56 (br. dd, J = 1.8, 15.8 Hz, 1 H, Ar*C*H=CH), 8.05 (br. d, J = 7.6 Hz, 1 H, 5-H), 8.34 (br. d, J = 7.6 Hz, 1 H, 8-H) ppm. ^{13}C NMR: δ = 18.8 (CH-*Me*), 56.0 (3-OMe), 60.3 (4-OMe), 63.4 (*N*-OMe), 108.1 (2-C), 123.4 (5-C), 124.1 (1-C), 127.2 (ArCH=*C*H), 127.8 (6-C), 129.1 (8-C), 129.2 (Ar*C*H=*C*H), 130.8 (7-C), 131.5 (9a-C),* 131.8 (2 C, 4a-C and 8a-C),# 132.9 (4b-C),# 139.4 (4-C),# 143.9 (*C*=NOMe), 154.0 (3-C) ppm. HRMS calcd. $C_{19}H_{20}NO_3$: 310.1438 [M^+]; found 310.1442.

5,6-Dimethoxy-2-methylindeno[1,2,3-*ij*]isoquinoline (2-methyltriclisine, 5): A solution of oxime **6a** (21 mg, 0.067 mmol) in 1,2-Cl_2-C_6H_4 (2.5 mL) was transferred to a microwave reactor tube; the tube was purged with argon, sealed and heated at 180 °C during 60 min, when absence of starting material was ascertained by TLC. The solution was submitted to column chromatography, giving **5** (15 mg, 81%) as a white solid; m.p. 126–128 °C (hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 2943, 2853, 1592, 1488, 1354, 1251, 1038, 999, 843, 744, 622 cm^{-1}. ^1H NMR: δ = 2.79 (s, 3 H, 2-Me), 3.97 (s, 3 H, 5-OMe), 4.04 (s, 3 H, 6-OMe), 6.86 (s, 1 H, 4-H), 7.23 (s, 1 H, 3-H), 7.38 (ddd, J = 1.5, 7.4, 7.5 Hz, 1 H, 9-H), 7.43 (ddd, J = 1.5, 7.4, 7.5 Hz, 1 H, 8-H), 7.94 (br. dd, J = 1.5, 7.4 Hz, 1 H, 7-H), 8.15 (dd, J = 1.5, 7.4 Hz, 1 H, 10-H) ppm. ^{13}C NMR: δ = 24.9 (Me-2), 56.3 (5-OMe), 61.4 (6-OMe), 104.2 (4-C), 115.4 (3-C), 121.6 (3a-C), 121.9 (10-C), 124.7 (7-C), 126.3 (10c-C), 128.2 (8-C), 129.6 (9-C), 131.2 (6a-C), 138.4 (10a-C), 139.2 (6b-C), 147.0 (6-C), 154.5 (2-C), 158.5 (10b-C), 159.1 (5-C) ppm. HRMS calcd. $C_{18}H_{16}NO_2$: 278.1176 [MH^+]; found 278.1179.

Supporting Information (see also the footnote on the first page of this article): Copies of the ^{13}C NMR spectra of the target compounds and synthetic intermediates are provided.

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