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


Keywords: Synthesis design / Nitrogen heterocycles / Natural products / Alkaloids / Azafluoranthenes / Electrocyclization

The synthesis of 2-methyltriclisine, an unnatural analog of the azafluoranthen alkaloid triclisine, is reported. The synthesis was achieved in 10 steps and 21% overall yield from 2-bromo-3,4-dimethoxybenzaldehyde, through the intermediate 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 azatria 6π-electron system formed by oximation of its carbonyl function.

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 azafluoranthen 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 Telticxicum peruvianum, together with teltixine (1f), isolated from T. peruvianum and T. glaziouiv[3c] and normimeluteine (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 eupolaridin (2a) and its N-oxides 2b, 2c that can be found in Annonaceae, as well as with the less widespread stephanoxocanes, such as stephanoxocanidine (3a) and eletefine (3b) and the tropolo-isoquinolines, exemplified by grandirubrine (4a) and inerubrine (4b).[4] Compounds carrying the latter two skeletons have been isolated from Menispermaceous plants, including species which are also sources of azafluoranthen alkaloids.[5a] Furthermore, azafluoranthen derivatives have been prepared as part of some synthetic efforts toward tropolo-isoquinolines,[5b,5c]

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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\cite{14a} and have been reported to possess antidepressant activity.\cite{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,\cite{3d} while related 4azafluoranthene derivatives have been shown to act as 5-hydroxytryptamine subclass 3 receptor (5-HT₃) agonists.\cite{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.\cite{7}

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

In pursuit of our interest in the elaboration of polycyclic tetrahydroisoquinoline-type natural products, their derivatives\cite{11} and bioactive analogs,\cite{12} herein we report the synthesis of 2-methyltriclisine (5), an unnatural analog of tricli-sine (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 6n-electron system as the final key transformation, which involves formation of the N–C bond. Synthesis of isoquinoline derivatives based on the formation of this bond is still one of the less exploited strategic alternatives toward constructing these heterocycles; however, it is currently receiving considerable attention.\cite{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.\cite{14a}

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.\cite{14a} We concluded that this sequence was excessively long, partly because of the need of introducing and removing activating and protecting groups. Therefore, and taking into account the technological and biomedical importance of fluoren-9-ones, their usefulness as synthetic intermediates and their occurrence as natural products\cite{15} we also decided to devise a new strategy toward 8.

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).\cite{16}

We conjectured that for our purpose, in either case known aldehydes 11a\cite{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 “di rect” arylation reactions inclines us toward exploring the intramolecular arylation alternative.

Therefore, the synthesis (Scheme 2) began with the treatment of iodoaldehyde 11a\cite{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.\cite{18}
the Pd(OAc)\textsubscript{2} after several attempts it was observed that submission of benzophenone starting material for a similar reaction sequence, furnishing and K\textsubscript{2}CO\textsubscript{3}, smoothly and consistently afforded employing ligand \(13\) as ligand in the presence of a mixture of KOAc and K\textsubscript{2}CO\textsubscript{3}, gave only 34\% yield of (\(°\)) ranging from 88 to 96\% after heating 22 h at 110 °C. On the other hand, (DMA) under Pd(PPh\textsubscript{3})\textsubscript{4} catalysis, employing DavePhos (\(13\)) as ligand in the presence of a mixture of KOAc and K\textsubscript{2}CO\textsubscript{3}, yielded 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.\textsuperscript{[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 \(^1\)H 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,\textsuperscript{[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 dealkylate methyl ethers located ortho or para to electron-withdrawing groups.\textsuperscript{[22b]} The preferred demethylation of the ortho-disubstituted methyl ether moiety\textsuperscript{[22a,23]} could arise from the out-of-plane preferred conformation adopted by the methyl group in these compounds, which may facilitate their reac-

![Scheme 2](image-url)

**Scheme 2.** Reagents and conditions: a) PhMgBr, THF, 0 °C→r.t. (12a, 85\%; 12b, 94\%); b) PDC, CH\textsubscript{2}Cl\textsubscript{2}, room temp., 15 h (10a, 93\%; 10b, 92\%); c) Pd(PPh\textsubscript{3})\textsubscript{4}, DavePhos (13), KOAc, K\textsubscript{2}CO\textsubscript{3}, DMA, 110 °C, 22 h (10a→\(8\), 34\%; 10b→\(8\), 88–96\%).

However, when cyclization of 10a was attempted using the Pd(OAc)\textsubscript{2}–triethanolamine reagent system,\textsuperscript{[19]} the dehalogenated starting material (10c)\textsuperscript{[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\textsubscript{3})\textsubscript{4} catalysis, employing DavePhos (13) as ligand in the presence of a mixture of KOAc and K\textsubscript{2}CO\textsubscript{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 accept a poisoning effect in the direct arylation reaction,\textsuperscript{[20a]} the analogous bromoaldehyde 11b\textsuperscript{[17e]} 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\textsubscript{3})\textsubscript{4}-catalyzed cyclization in DMA, employing ligand 13 in a mixture of KOAc and K\textsubscript{2}CO\textsubscript{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\textsubscript{2}CO\textsubscript{3}, while use of Pd(OAc)\textsubscript{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,\textsubscript{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\textsuperscript{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.\textsuperscript{[20b–20d]}

Then, reductive elimination of Pd\textsuperscript{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 phosphine 13 may facilitate both, the oxidative addition step and also dissociation of the halide, yielding a more reactive cationic palladium(II) species (A).

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 dealkylate methyl ethers located ortho or para to electron-withdrawing groups.\textsuperscript{[22b]} The preferred demethylation of the ortho-disubstituted methyl ether moiety\textsuperscript{[22a,23]} could arise from the out-of-plane preferred conformation adopted by the methyl group in these compounds, which may facilitate their reac-

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Pd source</th>
<th>Reagents and conditions</th>
<th>Product (% yield)</th>
</tr>
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<tbody>
<tr>
<td>10a</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>N(CH\textsubscript{2}CH\textsubscript{2}OH)\textsubscript{3}, microwave, 120 °C, 10 min</td>
<td>10c (84)</td>
</tr>
<tr>
<td>10a</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>KOAc, K\textsubscript{2}CO\textsubscript{3}, 13, DMA, 110 °C, 8 h</td>
<td>8 (34)</td>
</tr>
<tr>
<td>10b</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>N(CH\textsubscript{2}CH\textsubscript{2}OH)\textsubscript{3}, microwave, 120 °C, 30 min</td>
<td>decomposition</td>
</tr>
<tr>
<td>10b</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>KOAc, 13, DMA, 135 °C, 4 h</td>
<td>8 (56)</td>
</tr>
<tr>
<td>10b</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>KOAc, K\textsubscript{2}CO\textsubscript{3}, 13, DMA, 110 °C, 22 h</td>
<td>8 (88–96)</td>
</tr>
</tbody>
</table>

[a] Bath preheated at the designated temperature.
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-Cl2-C6H4 (180°C, 2 h) and in Ph2O (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-Cl2-C6H4. This gave allylfluorenone derivative 16 in 80% yield. The product, which displayed 2-H as a singlet in its 1H NMR spectrum (δH = 6.46 ppm), was uneventfully alkylated under standard conditions (Scheme 4), with MeI in refluxing EtOH to which excess K2CO3 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 1-allylfluoren-9-one 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 PdCl2(MeCN)2 in refluxing CH2Cl2 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-Cl2-C6H4, 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 1H and 13C 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 (δH = 3.97 ppm) is more shielded than 6-OMe (δH = 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 intermediary of known 3,4-dimethoxyfluoren-9-one (8) and without
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 benzyldiol 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 CH2Cl2 was prepared by a 4 h reflux of the solvent over P2O5 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 Na2SO4 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 compounds gave single spots on TLC plates run in different hexane/EtOAc and CH2Cl2/toluene solvent systems. Chromatographic experiments (COSY, HMBC and HMQC) were also employed. Pairs of signals marked with asterisks (*) or hashes (#) indicate experiments (COSY, HMBC and HMQC) were also employed. All compounds gave single spots on TLC plates run in different hexane/EtOAc and CH2Cl2/toluene solvent systems. Chromatographic experiments (COSY, HMBC and HMQC) were also employed. Pairs of signals marked with asterisks (*) or hashes (#) indicate experiments (COSY, HMBC and HMQC) were also employed.

Melting points were determined on a 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 13C NMR spectra were acquired in CDCl3 in a Bruker Avance spectrometer (300.13 and 75.48 MHz for 1H and 13C, respectively). The chemical shifts are reported in parts per million (δ) ppm. 1H NMR: δ = 3.87 (s, 3 H, 3-OMe), 3.93 (s, 3 H, 4-OMe), 6.95 (d, 2 J, 7.9 Hz, 2 H, 2’-H and 5’-H) ppm. 13C NMR: δ = 56.1 (4-Ome), 60.3 (3-Ome), 78.7 (C-OMe), 98.2 (2-C), 112.5 (5-C), 124.1 (6-C). The fully decoupled 13C NMR spectra. In special cases, 2D-NMR experiments were performed with a Perkin–Elmer Q-700 spectrometer equipped with an apolar fused silica capillary column (30 μ×0.25 mm), coated with 5% phenyl- and 95% dimethyl-polyisiloxane (DB-5, coating thickness 0.25 μm). High-resolution mass spectroscopic data were obtained from the University of California, Riverside (USA). For the determination of fluorene-9-one 8 was monitored employing a Shimadzu model 14B gas chromatograph fitted with a J&W Scientific 30 m×0.25 mm polydimethylsiloxane capillary column and a flame ionization detector. Hydrogen (1 mL/min) was employed as carrier gas. Chromatographic parameters were: T1 = 270 °C; T1= 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 mL, 6.0 mL). After 1 h, the reaction was treated with saturated NH4Cl 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 Na2SO4 and subjected to chromatography, giving (2-iodo-3,4-dimethoxyphenyl)methyl alcohol (12a) (594 mg, 85%), as a white solid; m.p. 123–125 °C (hexane/EtOAc). IR (KBr): ν = 3469, 2961, 1590, 1476, 1393, 1378, 1014, 926, 814, 729 (and 661) cm⁻¹. 1H NMR: δ = 2.51 (br, s, 1 H, w1/2 = 7.2 Hz, OH), 3.83 (s, 3 H, 3-Ome), 3.86 (s, 3 H, 4-Ome), 6.10 (s, 1 H, ArCHO), 6.88 (d, J = 8.6 Hz, 1 H, 1-H), 7.15 (d, J = 8.6 Hz, 1 H, 6-H), 7.25–7.42 (m, 5 H, ArH) ppm. 13C NMR: δ = 56.1 (4-Ome), 60.3 (3-Ome), 78.7 (C-OMe), 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 CH2Cl2 (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)methylmethanol 10a (375 mg, 93%), as a yellowish solid; m.p. 117–119 °C (hexane/EtOAc). IR (KBr): ν = 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, 1-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. 13C NMR: δ = 56.1 (4-Ome), 60.3 (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), Davaphos (3.7 mg, 0.0095 mmol) and K2CO3 (26 mg, 0.19 mmol) were successively added to a solution of Pd(PPh3)4 (0.0095 mmol) in anhydrous CH2Cl2 (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 MgSO4 and chromatographed, furnishing the benzophenone derivative 10c (43 mg, 19%) as a white solid, m.p. 88–90 °C (hexane/EtOAc; ref.17c 86–90 °C). IR (KBr): ν = 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),
was successively treated with anhydrous KOAc (219 mg, 2.23 mmol), DavePhos (44 mg, 0.11 mmol) and K2CO3 (309 mg, 2.24 mmol) and the resulting suspension was stirred at room temperature during 15 min, when a solution of benzenophene 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 MgSO4 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 iodoaldehyde 12a through the intermediacy of 2-idoazobenzene derivative 10a.

**FULL PAPER**

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found 267.1017. Increasing solvent polarity allowed the isolation of desired resigoisomer 7 (119 mg, 52% overall yield), as a yellowish solid; m.p. 78–79 °C (hexane/EtOAc). IR (KBr): v = 3022, 2951, 2847, 1699, 1560, 1497, 1365, 1253, 1150, 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, ArOCH₂), 5.28 (dd, J = 1.4, 10.4 Hz, 1 H, CH = CH₂), 5.42 (dd, J = 1.4, 17.2 Hz, 1 H, CH = CH₂), 6.14 (dd, J = 5.9, 10.4, 17.2 Hz, 1 H, CH = CH₂), 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. 13C NMR: δ = 56.2 (3-O-Me), 73.7 (Ar-CH₂), 111.2 (2-C), 118.3 (CH = CH₂), 121.4 (1-C), 123.8 (8-C), 124.2 (5-C), 128.9 (9-C), 128.7 (6-C), 133.8 (CH = CH₂), 134.7 (7-C), 135.2 (8a-C), 136.7 (4a-C), 142.6 (4b-C), 143.3 (4-C), 159.3 (1-3-C), 192.5 (C(O)) ppm. HRMS calc. C₁₉H₁₈O₃: 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-C₂H₅OH (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): v = 3411, 3069, 2970, 2830, 1625, 1529, 1466, 1385, 1249, 1129, 1004, 906, 851, 740, 666 cm⁻¹. 1H NMR: δ = 3.80 (dd, J = 1.3, 5.2 Hz, 2 H, ArCH₂), 3.94 (s, 3 H, 3-OME), 5.06 (dd, J = 1.4, 3.0, 10.0 Hz, 1 H, CH = CH₂), 5.13 (dd, J = 1.4, 3.0, 17.1 Hz, 1 H, CH = CH₂, 5.92 (s, 1 H, OH), 5.98 (add, J = 5.3, 5.3, 10.0, 17.1 Hz, 1 H, CH = CH₂), 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), 7.80 (br. d, J = 7.5 Hz, 1 H, 8-H), 7.83 (br. d, J = 7.5 Hz, 1 H, 5-H) ppm. 13C NMR: δ = 34.9 (Ar-CH₂), 56.4 (3-O-Me), 111.0 (2-C), 116.0 (CH = CH₂), 132.3 (4a-C), 124.0 (5-C), 124.5 (1-C), 128.0 (7-C), 128.5 (9-C), 134.2 (6-C), 134.9 (8a-C), 135.1 (4a-C), 136.5 (CH = CH₂), 140.0 (4b-C), 142.2 (4-C), 152.3 (3-C), 193.6 (C(O)) ppm. HRMS calc. C₁₉H₁₈O₃: 267.1016 [MH⁺]; found 267.1017.

1-Allyl-3,4-dimethoxyfluoren-9-one (17): A solution of allylphenol 16a (5 mL) and extracted with CHCl₃ (5 ml) was added to a stirred solution of allylphenol 16a (52 mg, 92 %), as a yellow solid; m.p. 126 °C. 1H NMR: δ = 3.83 (dd, J = 1.4, 6.6 Hz, 2 H, ArCH₂), 3.93 (s, 3 H, 3-OME), 3.94 (s, 3 H, 3-OME), 4.04 (s, 3 H, 6-OMe), 6.28 (dq, J = 6.6, 15.8 Hz, CH = CH₂), 6.49 (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, ArCH = CH₂), 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. 13C NMR: δ = 18.8 (CH = CH₂), 56.0 (3-O-Me), 60.3 (4-O-Me), 63.4 (3-O-Me), 108.1 (2-C), 123.4 (5-C), 124.1 (1-C), 127.2 (ArCH = CH₂), 127.8 (6-C), 129.1 (8-C), 129.2 (1-C), 130.8 (7-C), 131.5 (9a-C), 131.8 (2-C, 4a-C and 8a-C), 139.4 (4b-C), 143.9 (C = O-OMe), 154.0 (3-C) ppm. HRMS calc. C₁₉H₁₇O₃: 291.1438 [M⁺]; found 291.1442.

(E)-1-Propenyl-3,4-dimethoxyfluoren-9-one (18): A stirred solution of 17 (58.4 mg, 0.208 mmol) in CH₂Cl₂ (5.0 mL) was treated with PbC₂H₃(MeCN)₂ (0.74 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): v = 2972, 2850, 1657, 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, 3H-, 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 = CH₂), 7.85 (dd, J = 1.4, 7.5 Hz, 1 H, 5-H) ppm. 13C NMR: δ = 18.8 (CH = Me), 56.0 (3-O-Me), 60.4 (4-O-Me), 107.0 (2-C), 122.5 (1-C), 123.4 (8-C), 123.7 (5-C), 126.1 (ArCH = CH₂), 128.6 (7-C), 129.9 (ArCH = CH₂), 131.4 (6-C), 135.6 (9a-C)*, 135.8 (8a-C)*, 136.0 (4a-C)*, 141.8 (4b-C)*, 143.9 (4-C)*, 158.4 (13-C), 193.2 (C(O)) ppm. HRMS calc. C₁₉H₁₇O₃: 287.1176 [MH⁺]; found 287.1179.

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

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Unnatural Analog of the Azafluoranthene Alkaloid Triclisine


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