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A New Route to Azafluoranthene Natural Products via Direct Arylation

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Abstract

Microwave-assisted direct arylation was successfully employed in the synthesis of azafluoranthene alkaloids for the first time. Direct arylation reactions on a diverse set of phenyltetrahydroisoquinolines produces the indeno[1,2,3-*ij*]isoquinoline nucleus *en route* to a high yielding azafluoranthene synthesis.

The method was used as a key step in the efficient preparation of the natural products rufescine and triclisine. As demonstrated herein, this synthetic approach should be generally applicable to the preparation of natural and un-natural azafluoranthene alkaloids as well as “azafluoranthene-like” isoquinoline alkaloids.

Keywords

Alkaloid; C-H Activation; Total Synthesis

Introduction

Azafluoranthene alkaloids have been identified as secondary metabolites in *Abuta*,^[1] *Triclisia*,^[2] *Telotoxicum*,^[3] *Stephania*,^[4] *Cissampelos*^[5] and *Pericampylus*^[6] species of the Menispermaceae family. Typical members include rufescine (**1**), imeluteine (**2**) and triclisine (**3**). This class of alkaloids shares some structural similarities to aporphine alkaloids such as nantenine (**4**).^[7] Naturally occurring members of both alkaloid classes have oxygenated functionalities (typically hydroxy, methoxy or methylenedioxy groups) decorating the biphenyl sub-structure.

Aporphine and azafluoranthene alkaloids have displayed interesting biological activities. Aporphine alkaloids have been shown to possess anticancer activity and there is evidence that this activity is exerted via induction of apoptosis, inhibiting cell proliferation and inhibiting DNA topoisomerase.^[8] Some members display acute hypotensive effects^[9] and anticonvulsant and antinociceptive activities have also been reported.^[10] In the realm of central nervous system (CNS) activity, aporphines have been studied as ligands for dopaminergic (D₁ and D₂), adrenergic and serotonergic receptors.^[11] The dopamine D₁/D₂ receptor agonist apomorphine is currently used as a treatment for Parkinson's Disease.^[10d] A number of aporphines are also known to be inhibitors of acetylcholinesterase, an enzyme that is the biological target of clinically available Alzheimer's Disease therapeutics.^[12] Our own work on aporphines have explored the synthesis and bioactivity of nantenine

derivatives as serotonin 5-HT_{2A} and α_{1A} adrenergic receptor antagonists,^[13] cytotoxic agents^[14] and acetylcholinesterase inhibitors.^[15]

As compared to aporphines, much fewer azafluoranthene natural products are known. Nevertheless, members of the azafluoranthene class of natural products have shown promising biological activity as anti-HIV^[6], antifungal and cytotoxic^[5, 16] agents. Recently, the cytotoxic activity of the azafluoranthene eupolauridine was attributed to targeting of DNA topoisomerase II^[17]. In addition to the biological activities mentioned, the extensive conjugation in molecules containing the azafluoranthene core endow them with interesting spectral properties. For this reason, they have been studied as potentially useful agents in luminescent and electroluminescent applications and devices.^[18]

A number of strategies have been investigated for the synthesis of azafluoranthenes. The construction of the aryl-aryl bond is usually a key step in reported methods. Pschorr-based cyclization,^[1a, 19] photocyclization^[20] and oxidative biaryl cyclization of isoquinoline precursors with toxic vanadium-based reagents^[21] have been successfully implemented in this regard. These methods suffer from low to moderate yields for the biaryl coupling step. Other strategies include: remote metalation cross-coupling on biaryl precursors,^[22] inverse electron demand Diels-Alder reaction of 3-carbomethoxy-2-pyrones^[23], intramolecular aza-Wittig condensation on fluorenone derivatives^[24] and microwave-assisted electrocyclization of aza-ene intermediates.^[25] These latter routes have the drawback of low-yielding steps or require long synthetic sequences. Synthetic approaches that are improved in efficiency and overall yield are desirable at this time, especially within the context of accessing diverse libraries of azafluoranthene analogs in order to fully exploit their bioactive potential.

We have recently deployed microwave-assisted direct arylation methods to prepare aporphine^[13c, 13e] and C-homoaporphine alkaloids.^[26] By analogy, we expected a similar strategy to be applicable to the synthesis of azafluoranthene alkaloids. It was envisaged that this method could offer improved alternatives to other reported methods in terms of efficiency and yields.

Results and Discussion

The key step in our anticipated synthesis of azafluoranthenes (**5**, Figure 2), required the preparation of a phenyltetrahydroisoquinoline intermediate (**6**). Such compounds are readily prepared via a Pictet-Spengler reaction with protected amine **7** and bromoaldehyde **8**. This strategy is analogous to the method pioneered by the Fagnou group for the synthesis of aporphine alkaloids in which intramolecular direct arylation was used to construct the biaryl bond of the aporphine core.^[27] In these prior works, the facility of various phosphine ligands for the direct arylation process under thermal conditions was demonstrated. The reaction was shown to be tolerant of a wide variety of substitution patterns (including electron-withdrawing groups) in both aromatic rings. We recently applied a variation of this method in which microwave irradiation was used (instead of thermal conditions) for the biaryl coupling step in the synthesis of aporphines.^[13c]

Efforts initially focused on optimization of the biaryl cyclization of the tetrahydroisoquinoline substrate **11**. Our interest in this regard stemmed from a desire to prepare analogs of the aporphine alkaloid nantenine (**4**), as part of our ongoing structure-activity relationship (SAR) studies on nantenine-like molecules at central nervous system (CNS) receptors.^[13a, 13b, 13e] Compound **11** was prepared from readily available^[28] **9**, and commercially available **10** as shown in Scheme 1.

With **11** in hand, we proceeded to evaluate the optimal combination of ligand, base and solvent required for microwave-assisted direct biaryl cyclization.

Table 1 summarizes the results of this study. Based on the demonstrated utility of Buchwald phosphine ligands such as PhDavePhos (ligand **A**) and DavePhos (ligand **B**) as well as di-tert-butyl(methyl)phosphine tetrafluoroborate (ligand **C**) for direct arylations to prepare similar (aporphine and homoaporphine) scaffolds,^[13c, 26–27, 29] we decided to investigate these ligands.

Ligand **A**, was ineffective in achieving high-yielding cyclization irrespective of the solvent or base tried (entries 1, 4 and 7). In the case of ligand, the best yield (41%, entry 8) was obtained using K₂CO₃ as base and DMSO as solvent. Cs₂CO₃ performed poorer than K₂CO₃ when either ligand **A** or **B** was used with DMSO as solvent (entries 4 and 5). Generally, the combination of K₂CO₃/DMSO gave higher yields than other base/solvent combinations used with a particular ligand (eg. compare entries 2 and 8; entries 3 and 9). Yields tended to be higher with ligand **C** as compared to the other ligands (entries 3, 6 and 9). The highest yield (91%) was obtained with a ligand **C**/K₂CO₃/DMSO combination.

Having optimized the direct arylation on **11**, we next turned our attention to examining the scope of the reaction with other substrates (**13a** – **13n**, Table 2). These substrates were prepared in a manner similar to that depicted in Scheme 1 (yields ranged from 70% – 95%). As shown in Table 2, high yields were obtained consistently with a variety of aryl ring substitution patterns, highlighting the utility of the method in producing the indeno[1,2,3-*ij*]isoquinoline core as a precursor to azafluoranthene natural products.

In continued explorations of the direct arylation reaction, coupling of substrate **15** (in which the aryl bromide partner is the incipient ring A of the azafluoranthene nucleus) was attempted. The impetus for inverting the arylation partners in this way was based on the ready availability of several benzaldehydes and heteroaromatic aldehydes (as inputs for the Pictet-Spengler reaction) for later library diversification. We found that this direct arylation proceeded to give **14d** but in poor yield (Scheme 2). This result was unexpected in light of current understanding of the mechanism of direct arylation.

Fagnou and others have provided evidence for a concerted metalation-deprotonation (CMD) pathway in direct arylation reactions with simple or electron deficient aromatics.^[30] In this context, electron-deficient aromatic rings (as the non-halide containing coupling partner) react more easily than electron-rich ones.^[30b] The acidity of the C-H bond in the unactivated ring is important; the more acidic this proton the more facile is deprotonation and the CMD pathway overall. On the basis of these considerations, we would expect that inversion of the coupling partners as in Scheme 2 should result in more facile coupling. Since this was not the case, it appears that inversion of partners in this intramolecular framework alters the mechanistic pathway in some way. In the absence of detailed mechanistic studies, we postulate that metalation of substrate **15** is less favorable for steric reasons (the halide is *ortho* to *two* substituents) and this combined with reduced C-H acidity in the arene ring, negatively impacts the CMD process. No attempts were made to optimize this reaction.

We then turned our attention to the transformation of the cyclized products **12** and **14** to azafluoranthenes. For this task, we focused on synthesis of **17** (Scheme 3) as well as the natural products rufescine (**1**) and triclisine (**3**). Our initial plan was to deprotect the *N*-ethyl carbamate group and then oxidize the resulting tetrahydroisoquinoline moiety to an isoquinoline.

However, when deprotection of the substrates **14n** and **14e** was attempted with aqueous NaOH/DMSO, this gave the hydroxylated products **16a** and **16b** respectively. After some experimentation, we found that deprotection of the carbamate and oxidation to the isoquinoline moiety could be effected in a single pot by heating the compounds with DBU in an atmosphere of dry oxygen.^[31] Mechanistically, this latter reaction involves removal of a benzylic proton, elimination of the carbamate group and oxidation of the dihydroisoquinoline thus formed. We are uncertain of the mechanism of the benzylic hydroxylation in the formation of **16a** and **16b** at present; our observations are however consistent with a requirement for oxygen and water for benzylic hydroxylation. A similar benzylic hydroxylation in the synthesis of 5,6,8,12b-tetrahydroisoindolo[1,2-A]isoquinolin-8-ones has been reported.^[32] Here, formation of a benzylic carbanion under the strongly basic conditions used (0.5M KOH/MeOH, air, reflux) is thought to precede the formation of a doubly benzylic radical species via reaction of the carbanion with molecular oxygen.^[32] It is possible that this mechanism is in operation in the case at hand. Interestingly, when **16a** or **16b** was heated with DBU/DMSO no reaction occurred, highlighting the fact that **16a** and **16b** are not formed as intermediates in the oxidation of **14n** and **14e** with DBU/DMSO to **1** and **3** respectively.

To further examine the utility of this method in constructing novel “azafluoranthene-like” isoquinoline-containing heterocycles, we decided to prepare compound **21**. Thus, compounds **18a** and **18b** were prepared using standard methods (see Experimental Section) and subjected to the optimized microwave-assisted arylation conditions (Scheme 4). Although inversion of the arylation partners did not give a high yield of biaryl coupled product in the synthesis of **14d** (Scheme 2), in the case of **18a**, compound **19** was obtained in 91% yield. (In this case, the increased C-H acidity of the pyridyl moiety as compared to the C-H acidity of the anisole moiety of **15**, probably compensates for the increased steric demand in metalation). As observed, the biaryl cyclization was accompanied by benzylic hydroxylation. Although moisture and air were rigorously excluded from this reaction in several attempts, we never isolated the un-hydroxylated cyclized product. Presumably, the pyridine moiety increases the propensity for benzylic oxidation of the initially formed cyclized product. This oxidation seems to occur very rapidly, probably during the work-up procedure. (We also observed similar benzylic hydroxylation of **14a** - **14n** but this was considerably slower; samples of **14a** - **14n** were 20 – 50% hydroxylated as estimated by TLC, after exposure to air for 24 hours). Attempts to achieve biaryl cyclization with substrate **18b** using our typical conditions were unsuccessful; the starting material was consumed but cyclized product could not be identified from the complex mixture produced.

Compound **19** was transformed to the dihydroisoquinoline **20** by treatment with TFA. The novel isoquinoline **21** was prepared by oxidation of **20** in the presence of DBU.

Conclusions

Microwave-assisted direct arylation is a powerful method for assembly of the indeno[1,2,3-*ij*]isoquinoline nucleus *en route* to azafluoranthene alkaloids. The arylation reaction under microwave conditions is rapid and is tolerant of a wide variety of substitution patterns in the aryl rings. Azafluoranthenes are easily accessed in 3 high-yielding steps (Pictet-Spengler reaction, microwave-assisted direct arylation and deprotection/oxidation) from readily available starting materials. This straightforward route offers considerable advantages over existing ones in terms of overall yields, efficiency and accessibility to compound diversity. Further work is continuing on the applicability of the method to other novel “azafluoranthene-like” isoquinoline scaffolds and assessment of the cytotoxicity and CNS receptor activity of these molecules. Our findings will be reported in due course.

Experimental Section

General

All moisture-sensitive and oxygen-sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere. Dry DMSO and all other reagents were purchased at the highest commercial quality from Aldrich and Fisher Scientific USA) and used without further purification, unless otherwise stated. A CEM Discover microwave reactor was used to carry out all direct arylation reactions. HRESIMS spectra were obtained using an Agilent 6520 QTOF instrument. ^1H NMR and ^{13}C NMR spectra were recorded using Bruker DPX-500 spectrometer (operating at 500 MHz for ^1H ; 125 MHz, for ^{13}C) using CDCl_3 as solvent unless stated otherwise. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^1H NMR and CDCl_3 (δ 77.0 ppm) in ^{13}C NMR unless stated otherwise. Chemical shift (δ 0.00 ppm) values are reported in parts per million and coupling constants in Hertz (Hz). Splitting patterns are described as singlet (s), doublet (d), triplet (t), and multiplet (m). Reactions were monitored by TLC with Whatman Flexible TLC silica gel G/UV 254 precoated plates (0.25 mm). TLC plates were visualized by UV (254 nm) and by staining in an iodine chamber. Flash column chromatography was performed with silica gel 60 (EMD Chemicals, 230–400 mesh, 0.063 mm particle size).

Synthesis of compound 11 - procedure for acyl Pictet-Spengler reaction

At 5 °C, concentrated sulfuric acid (0.5 mL) was added dropwise to a solution of carbamate **9**, (0.253 g, 1 mmol) and aldehyde **10** (0.229 g, 1 mmol) in acetic acid (5 mL). After stirring at room temperature for 2h, the reaction mixture was poured onto crushed ice-water and extracted with dichloromethane (10 mL). The organic layer was washed sequentially with water (10 mL) and brine (10 mL), dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with gradient elution in 10% – 30% ethyl acetate/hexanes mixtures to yield **11** (0.360 g, 78%). Compounds **13a-13n**, **15** and **18b** were prepared in a similar manner. Compound **18a** was prepared via a Bischler-Napieralki reaction as described below.

Synthesis of compound 18a—

Step 1: A solution of isonicotinic acid (0.147 g, 1.2 mmol) and 1,10-carbonyldiimidazole (0.194 g, 1.2 mmol) in anhydrous THF (10 mL) was stirred at 0 °C for 1.5 h and then, at room temperature for 1h. The mixture was cooled in an ice-bath and stirred for 1h. Then 2-(3-bromo-4,5-dimethoxyphenyl)ethanamine (0.260 g, 1 mmol) was added and the solution was stirred at 0 °C for 4 h and left stirring overnight at room temperature. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (20 mL) and washed with water (20 mL), saturated NaHCO_3 solution (10 mL), then with water (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This gave the crude product as a pale yellow gummy liquid (0.248 g, 68%).

Steps 2–4: To a mixture of the amide above (0.182 g, 0.5 mmol), P_2O_5 (1 g) in toluene (5 mL) was added $POCl_3$ and refluxed for 3 h. The solvent was evaporated under reduced pressure. The resulting solid was dissolved in water and carefully basified with solid $NaHCO_3$. Once the liberation of CO_2 had ceased, the aqueous layer was extracted with dichloromethane (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and was used in the next step without further purification.

To a magnetically stirred ice-cooled solution of the crude imine from the previous reaction in a mixture of dry MeOH (10 mL), was added $NaBH_4$ (0.174 g, 0.5 mmol) in three portions over 10 min. The reaction mixture was stirred at 0 °C for 2 h. The mixture was diluted with water and extracted with dichloromethane (5 mL). The combined organic layer dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude amine product was used in the next step without further purification.

To a solution of crude amine (0.174 g, 0.5 mmol) dissolved in dry dichloromethane (5 mL) was added DIPA (0.101 g, 1 mmol), DMAP (0.06 g, 0.05 mmol), and *tert*-butyl carbamate (0.087 g, 0.75 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 24 h, quenched with water (10 mL), and extracted with dichloromethane (10 mL). The organic layer was washed with water (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude product, on column chromatography over silica gel using EtOAc/Hexanes (20:80) as eluant, furnished compound **18a** (80 mg, 35.7%).

Compound 11—Yield 0.036 g (78%), white solid, R_f = 0.66 (silica gel, hexanes/EtOAc, 6:4), m.p. 117–119 °C. 1H NMR ($CDCl_3$): δ = 1.23 (t, J = 6.5 Hz, 3H), 2.75 (m, 1H), 2.96 (m, 1H), 3.37 (m, 1H), 3.75 (s, 3H), 3.86 (s, 3H), 4.16 (m, 3H), 5.92 (s, 1H), 5.93 (s, 1H), 6.36 (br. s, 1H), 6.49 (br. s, 1H), 6.51 (s, 1H), 6.65 (s, 1H), 7.05 (s, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.3, 39.4, 55.9 ($\times 2$), 57.2, 61.6, 101.8, 109.2, 110.4, 111.3 ($\times 2$), 112.8 ($\times 2$), 114.4, 126.6, 127.2, 147.4, 147.7, 148.0, 155.9. HRESIMS calculated for $C_{21}H_{23}BrNO_6$ $[M+H]^+$ 464.0703; found 464.0700.

Compound 13a—Yield 0.036 g (76%), colourless oil, R_f = 0.66 (silica gel, hexanes/EtOAc, 6:4). 1H NMR ($CDCl_3$): δ = 1.24 (t, J = 6.5 Hz, 3H), 2.79 (m, 1H), 2.98 (m, 1H), 3.40 (m, 1H), 3.69 (s, 3H), 3.75 (s, 3H), 3.89 (s, 6H), 4.16 (q, J = 6.5 Hz, 2H), 4.27 (m, 1H), 6.37 (br. s, 1H), 6.53 (br. s, 1H), 6.55 (s, 1H), 6.67 (s, 1H), 7.08 (s, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.4, 39.6, 55.87, 55.90, 55.95, 56.1, 57.1, 61.6, 110.5, 111.2, 112.0, 114.3, 115.5, 126.6, 127.4, 135.4, 147.7, 147.9, 148.4, 148.7, 156.0. HRESIMS calculated for $C_{22}H_{27}BrNO_6$ $[M+H]^+$ 480.0944; found 480.0938.

Compound 13b—Yield 0.030 g (68%), white solid, R_f = 0.68 (silica gel, hexanes/EtOAc, 6:4), m.p. 126–128 °C. 1H NMR ($CDCl_3$): δ = 1.23 (m, 3H), 2.82 (m, 1H), 2.97 (m, 1H), 3.42 (m, 1H), 3.76 (s, 3H), 3.90 (s, 3H), 4.16 (m, 3H), 6.41 (br. s, 1H), 6.55 (s, 1H), 6.67 (s, 1H), 6.77 (br. s, 1H), 6.86 (dd, J = 8.0, 13.7 Hz, 1H), 7.59 (dd, J = 5.5, 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.4, 39.6, 55.9 ($\times 2$), 57.3, 61.7, 110.3, 111.4 ($\times 2$), 116.0, 116.2, 126.5, 126.7, 134.2, 147.8, 148.2, 155.9, 161.1, 163.1. ^{19}F NMR ($CDCl_3$): δ = -114.5 (d, J = 375 Hz). HRESIMS calculated for $C_{20}H_{22}BrFNO_4$ $[M+H]^+$ 438.0638; found 438.0636.

Compound 13c—Yield 0.029 g (67%), colourless oil, R_f = 0.37 (silica gel, hexanes/EtOAc, 6:4). 1H NMR ($CDCl_3$): δ = 1.17 (m, 3H), 2.03, (br. s, 1H), 2.72 (m, 1H), 2.91 (m, 1H), 3.38 (m, 1H), 3.71 (s, 3H), 3.82 (s, 3H), 4.08 (m, 4H), 6.31 (s, 1H), 6.59 (m, 3H), 7.39 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.5, 28.2, 39.6, 55.8 ($\times 2$), 57.3, 61.9, 110.4,

111.2 (×2), 113.4 (×2), 116.5, 126.5, 127.0, 133.7, 144.9, 147.6, 147.9, 156.5. HRESIMS calculated for $C_{20}H_{23}BrNO_5$ $[M+H]^+$ 436.0681; found 436.0679.

Compound 13d—Yield 0.032g (72%), colourless oil, R_f = 0.67 (silica gel, hexanes/EtOAc, 6:4). 1H NMR ($CDCl_3$): δ = 1.23 (m, 3H), 2.80 (m, 1H), 2.95 (m, 1H), 3.43 (m, 1H), 3.71 (s, 3H), 3.76 (s, 3H), 3.89 (s, 3H), 4.15 (m, 4H), 6.39 (br. s, 1H), 6.68 (m, 4H), 7.52 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.5, 28.3, 39.3, 55.4, 55.86, 55.90, 57.3, 61.6, 110.4, 111.25, 111.28 (×2), 113.7, 126.6, 127.1, 133.6, 147.8, 148.00, 148.02, 156.1, 159.2. HRESIMS calculated for $C_{21}H_{25}BrNO_5$ $[M+H]^+$ 450.0838; found 450.0834.

Compound 13e—Yield 0.031g (73.5%), colourless oil, R_f = 0.60 (silica gel, hexanes/EtOAc, 6:4). 1H NMR ($CDCl_3$): δ = 1.23 (m, 3H), 2.79 (m, 1H), 2.98 (m, 1H), 3.40 (m, 1H), 3.74 (s, 3H), 3.89 (s, 3H), 4.16 (m, 3H), 6.49 (br. s, 1H), 6.55 (s, 1H), 6.67 (s, 1H), 7.05 (br. s, 1H), 7.12 (m, 1H), 7.19 (m, 1H), 7.63 (d, J = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.2, 39.3, 55.9 (×2), 57.3, 61.6, 110.5, 111.3 (×2), 126.7, 127.2, 127.6, 128.8, 130.0, 133.1, 147.7, 148.03, 148.04, 155.9. HRESIMS calculated for $C_{20}H_{23}BrNO_4$ $[M+H]^+$ 420.0732; found 420.0728.

Compound 13f—Yield 0.028g (67%), white solid, R_f = 0.40 (silica gel, hexanes/EtOAc, 6:4), m.p. 129–131 °C. 1H NMR ($CDCl_3$): δ = 1.30 (m, 3H), 2.80 (m, 1H), 2.94 (m, 1H), 3.41 (m, 1H), 3.77 (s, 3H), 4.14 (m, 3H), 5.68 (s, 1H), 6.49 (br. s, 1H), 6.54 (s, 1H), 6.77 (m, 2H), 6.87 (m, 1H), 7.60 (dd, J = 5.5, 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.0, 39.5, 55.9, 57.4, 61.7, 109.7, 114.5, 115.9, 116.1, 117.2, 117.9, 125.9, 127.4, 134.2, 144.9, 145.5, 155.9, 161.9. ^{19}F NMR ($CDCl_3$): δ = -113.5 (d, J = 360 Hz). HRESIMS calculated for $C_{19}H_{20}BrFNO_4$ $[M+H]^+$ 420.0481; found 420.0477.

Compound 13g—Yield 0.030g (68%), white solid, R_f = 0.38 (silica gel, hexanes/EtOAc, 6:4), m.p. 105–107 °C. 1H NMR ($CDCl_3$): δ = 1.22 (m, 3H), 2.77 (m, 1H), 2.93 (m, 1H), 3.42 (m, 1H), 3.71 (s, 3H), 3.77 (s, 3H), 4.15 (m, 3H), 5.56 (m, 1H), 6.39 (br. s, 1H), 6.56 (s, 1H), 6.61 (br. s, 1H), 6.69 (dd, J = 3.5, 8.5 Hz, 1H), 6.74 (s, 1H), 7.51 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.0, 39.4, 55.3, 55.9, 57.5, 61.6, 109.9, 113.8, 114.3 (×2), 115.7, 126.5 (×2), 127.4 (×2), 133.5, 143.8, 145.4, 155.9. HRESIMS calculated for $C_{20}H_{23}BrNO_5$ $[M+H]^+$ 436.0681; found 436.0679.

Compound 13h—Yield 0.028g (70%), colourless oil, R_f = 0.39 (silica gel, hexanes/EtOAc, 6:4). 1H NMR ($CDCl_3$): δ = 1.20 (m, 3H), 2.71 (m, 1H), 2.90 (m, 1H), 3.34 (m, 1H), 3.71 (s, 3H), 4.14 (m, 3H), 5.70 (s, 1H), 6.43 (br. s, 1H), 6.50 (s, 1H), 6.72 (s, 1H), 7.02 (br. s, 1H), 7.09 (m, 1H), 7.17 (m, 1H), 7.60 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.0, 38.4, 55.9, 57.4, 61.6, 109.9, 114.3 (×2), 124.2, 126.7, 127.5, 128.7, 129.8, 130.8, 133.1, 144.6, 145.4, 155.9. HRESIMS calculated for $C_{19}H_{21}BrNO_4$ $[M+H]^+$ 408.0630; found 408.0630.

Compound 13i—Yield: 0.026g (62%), colourless oil, R_f = 0.40 (silica gel, hexanes/EtOAc, 6:4). 1H NMR ($CDCl_3$): δ = 1.21 (m, 3H), 2.82 (m, 1H), 2.95 (m, 1H), 3.42 (dd, J = 10.5, 10.5 Hz, 1H), 3.89 (s, 3H), 4.14 (m, 3H), 5.57 (s, 1H), 6.36 (br. s, 1H), 6.58 (s, 1H), 6.66 (s, 1H), 6.76 (br. s, 1H), 6.84 (m, 1H), 7.56 (dd, J = 5.5, 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.6, 39.8, 55.9, 57.2, 61.8, 110.5, 113.5, 115.9, 116.1, 126.3, 127.5, 134.3, 144.0, 146.14, 146.14, 156.3, 160.9, 163.2. ^{19}F NMR ($CDCl_3$): δ = -114.2 (d, J = 250 Hz). HRESIMS calculated for $C_{19}H_{20}BrFNO_4$ $[M+H]^+$ 424.0553; found 424.0553.

Compound 13j—Yield: 0.032g (70%), white solid, R_f = 0.36 (silica gel, hexanes/EtOAc, 6:4), m.p. 161–163 °C. 1H NMR ($CDCl_3$): δ = 1.24 (m, 3H), 2.77 (m, 1H), 2.94 (m, 1H),

3.39 (m, 1H), 3.89 (s, 3H), 4.15 (m, 3H), 5.48 (s, 1H), 5.94 (m, 2H), 6.33 (br. s, 1H), 6.55 (m, 2H), 6.64 (s, 1H), 7.05 (s, 1H). ^{13}C NMR (CDCl_3): δ = 14.2, 28.6, 39.7, 55.9, 57.1, 61.7, 101.8 ($\times 2$), 109.2, 110.7 ($\times 2$), 112.6, 113.6, 114.5, 126.0, 136.2, 144.3, 145.8, 147.4, 155.9. HRESIMS calculated for $\text{C}_{20}\text{H}_{21}\text{BrNO}_6$ $[\text{M}+\text{H}]^+$ 452.0529; found 452.0527.

Compound 13k—Yield: 0.032g (73%), colourless oil, R_f = 0.38 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.18 (m, 3H), 2.75 (m, 1H), 2.92 (m, 1H), 3.40 (m, 1H), 3.66 (s, 3H), 3.85 (s, 3H), 4.11 (m, 3H), 5.70 (br. s, 1H), 6.33 (br. s, 1H), 6.65 (m, 4H), 7.46 (d, J = 9.0 Hz, 1H). ^{13}C NMR (CDCl_3): δ = 14.6, 28.6, 39.8, 55.3, 55.9, 57.2, 61.7, 110.7, 111.3, 113.7, 114.9, 115.1, 121.4, 126.0, 127.9, 133.6, 144.3, 145.7, 156.0, 158.9. HRESIMS calculated for $\text{C}_{20}\text{H}_{23}\text{BrNO}_5$ $[\text{M}+\text{H}]^+$ 436.0681; found 436.0676.

Compound 13l—Yield: 0.034g (73%), colourless oil, R_f = 0.35 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.20 (m, 3H), 2.25 (s, 1H), 2.76 (m, 1H), 2.96 (m, 1H), 3.39 (m, 1H), 3.67 (s, 3H), 3.86 (s, 6H), 4.14 (q, J = 6.5 Hz, 2H), 4.28 (br. s, 1H), 6.29 (br. s, 1H), 6.55 (s, 1H), 6.56 (s, 1H), 6.63 (s, 1H), 7.03 (s, 1H). ^{13}C NMR (CDCl_3): δ = 14.6, 28.8, 39.9, 55.90, 55.95, 56.1, 57.0, 61.6, 110.5 ($\times 2$), 112.2, 113.6, 114.6, 115.4, 125.9, 128.1, 144.3, 145.6, 148.5, 148.6, 155.9. HRESIMS calculated for $\text{C}_{21}\text{H}_{25}\text{BrNO}_6$ $[\text{M}+\text{H}]^+$ 466.0787; found 466.0785.

Compound 13m—Yield: 0.042g (82%), colourless oil, R_f = 0.62 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.13 (m, 3H), 2.62 (m, 1H), 3.08 (m, 1H), 3.34 (s, 3H), 3.51 (m, 1H), 3.62 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 4.07 (m, 2H), 4.38 (br. s, 1H), 6.14 (s, 1H), 6.33 (br. s, 1H), 6.75 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H). ^{13}C NMR (CDCl_3): δ = 14.6, 23.3, 39.9, 55.8, 55.9, 57.1, 59.6, 60.90, 60.94, 61.3, 105.7, 112.7, 116.8, 121.3, 127.6, 130.9, 136.8, 140.7, 148.4, 150.6, 151.6, 152.9, 156.1. HRESIMS calculated for $\text{C}_{23}\text{H}_{29}\text{BrNO}_7$ $[\text{M}+\text{H}]^+$ 510.1049; found 510.1048.

Compound 13n—Yield: 0.038g (80%), white solid, R_f = 0.67 (silica gel, hexanes/EtOAc, 6:4), m.p. 78–80 °C. ^1H NMR (CDCl_3): δ = 1.23 (m, 3H), 2.81 (m, 2H), 3.35 (m, 1H), 3.71 (s, 3H), 3.73 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 4.16 (m, 3H), 6.41 (br. s, 2H), 6.59 (br. s, 1H), 6.70 (dd, J = 3.0, 8.5 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H). ^{13}C NMR (CDCl_3): 14.6, 22.4, 39.2, 55.4, 55.9, 57.4, 60.7, 60.8, 61.6, 106.5, 113.6, 114.8, 115.9, 116.2, 121.1, 130.6, 133.6, 140.9, 150.9, 152.0, 155.9, 158.9. HRESIMS calculated for $\text{C}_{22}\text{H}_{27}\text{BrNO}_6$ $[\text{M}+\text{H}]^+$ 480.0944; found 480.0939.

Compound 15—1:1 Mixture of rotamers (signals for one rotamer reported). Yield 0.037g (83%), colourless oil, R_f = 0.7 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.29 (m, 3H), 2.69 (m, 1H), 2.96 (m, 1H), 3.13 (m, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 4.30 (m, 2H), 4.38 (m, 1H), 6.51 (s, 1H), 6.76 (m, 4H), 7.20 (m, 1H). ^{13}C NMR (CDCl_3): δ = 14.8, 28.2, 55.1, 56.1, 57.2, 57.4, 60.6, 61.7, 111.6, 112.3, 114.4, 119.5, 120.6, 127.5, 129.1, 132.5, 142.3, 145.0, 152.3, 155.0, 159.1. HRESIMS calculated for $\text{C}_{21}\text{H}_{25}\text{BrNO}_5$ $[\text{M}+\text{H}]^+$ 450.0838; found 450.0835.

Compound 18a—Mixture of rotamers (signals for one rotamer reported). Yield 0.080g (35.7%), colourless oil, R_f = 0.2 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.55 (m, 9H), 2.64 (m, 1H), 2.93 (m, 1H), 3.05 (m, 1H), 3.83 (m, 1H), 3.85 (s, 3H), 3.89 (s, 3H), 6.63 (s, 1H), 6.74 (m, 1H), 7.06 (m, 2H), 8.51 (m, 2H). ^{13}C NMR (CDCl_3): δ = 28.4, 37.3, 38.4, 55.8, 56.1, 60.6, 76.8, 77.1, 80.5, 112.0, 119.0, 119.5, 122.7, 126.5, 126.6, 132.8, 145.3, 149.8, 150.1, 152.8, 154.8. HRESIMS calculated for $\text{C}_{21}\text{H}_{26}\text{BrN}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 449.0998; found 449.0996.

Compound 18b—Yield 0.034g (82%), colourless oil, R_f = 0.2 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.18 (m, 3H), 2.93 (m, 2H), 3.46 (m, 1H), 3.73 (s, 3H), 3.86 (s, 3H), 4.12 (m, 3H), 6.36 (br. s, 1H), 6.55 (d, J = 4.5 Hz, 1H), 6.66 (d, J = 4.5 Hz, 1H), 7.03 (br. s, 1H), 8.37 (s, 1H), 8.75 (s, 1H). ^{13}C NMR (CDCl_3): δ = 14.5, 28.3, 40.0, 55.9, 56.7, 61.9, 109.9, 111.44, 122.3, 125.4, 126.7, 148.2, 149.1, 153.4, 156.5. HRESIMS calculated for $\text{C}_{19}\text{H}_{22}\text{BrN}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 421.0685; found 421.0687.

Synthesis of compound 12 - procedure for microwave-assisted direct arylation reaction

In a microwave reaction vial, dihydroisoquinoline **11** (0.046 g, 0.1 mmol), $\text{Pd}(\text{OAc})_2$ (0.0044g, 0.02 mmol), ligand **C** (0.0099 g, 0.04 mmol) and K_2CO_3 (0.0276 g, 0.2 mmol) were added and dissolved in Ar-purged anhydrous, degassed DMSO (0.5 mL). The mixture was irradiated in a CEM Discover microwave reactor for 5 min at 135 °C with the power level at 300W. After cooling to room temperature, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (5 mL). The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography eluted with 10 – 20% EtOAc/hexanes. This furnished the cyclized product **12**. Compounds **14a-14n**, **16a**, **16b** and **19** were obtained in a similar manner.

Compound 12—Yield 0.034g (91%), colourless oil, R_f = 0.67 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.42 (t, J = 7.0 Hz, 3H), 2.66 (m, 2H), 2.88 (m, 1H), 3.93 (s, 3H), 3.98 (s, 3H), 4.38 (m, 2H), 4.51 (m, 1H), 5.46 (s, 1H), 6.02 (d, J = 1.2 Hz, 1H), 6.03 (d, J = 1.2 Hz, 1H), 6.61 (s, 1H), 7.51 (s, 2H). ^{13}C NMR (CDCl_3): δ = 14.9, 29.8, 44.8, 56.5, 58.5, 60.7, 62.0, 101.3, 104.3, 108.0, 108.6 ($\times 2$), 131.3, 132.8, 133.7, 142.1, 142.7, 146.9, 147.6, 153.3, 158.1. HRESIMS calculated for $\text{C}_{21}\text{H}_{22}\text{NO}_6$ $[\text{M}+\text{H}]^+$ 384.1369; found 384.1365.

Compound 14a—Yield 0.0356g (89%), colourless oil, R_f = 0.67 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.43 (t, J = 6.5 Hz, 3H), 2.67 (m, 2H), 2.90 (m, 1H), 3.90 (s, 3H), 3.96 (s, 3H), 4.00 (s, 6H), 4.38 (m, 2H), 4.52 (m, 1H), 5.50 (s, 1H), 6.62 (s, 1H), 7.58 (br. s, 2H). ^{13}C NMR (CDCl_3): δ = 14.9, 29.9, 44.8, 56.1, 56.2, 56.4, 58.7, 60.6, 61.9, 106.6, 108.8 ($\times 2$), 110.3, 131.4, 131.6, 133.7, 140.7, 142.7, 148.3, 149.2, 153.3, 157.9. HRESIMS calculated for $\text{C}_{22}\text{H}_{26}\text{NO}_6$ $[\text{M}+\text{H}]^+$ 400.1755; found 400.1753.

Compound 14b—Yield 0.031g (86%), colourless oil, R_f = 0.7 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.43 (t, J = 6.7 Hz, 3H), 2.69 (m, 2H), 2.89 (m, 1H), 3.94 (s, 3H), 3.99 (s, 3H), 4.39 (t, J = 6.7 Hz, 2H), 4.52 (m, 1H), 5.53 (s, 1H), 6.67 (s, 1H), 7.09 (m, 1H), 7.71 (br. s, 1H), 7.96 (dd, J = 5.5, 8.4 Hz, 1H). ^{13}C NMR (CDCl_3): δ = 14.7, 29.8, 44.6, 56.4, 58.69, 58.71, 60.6, 62.1, 109.4, 114.9, 115.1, 124.4, 131.5, 133.5, 134.9, 143.2, 150.0, 153.4, 157.9, 162.0. ^{19}F NMR (CDCl_3): δ = -114.1 (d, J = 375 Hz). HRESIMS calculated for $\text{C}_{20}\text{H}_{21}\text{FNO}_4$ $[\text{M}+\text{H}]^+$ 358.1449; found 358.1450.

Compound 14c—Yield 0.029g (81%), colourless oil, R_f = 0.38 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.41 (t, J = 7.0 Hz, 3H), 1.70 (br. s, 1H), 2.67 (m, 2H), 2.89 (m, 1H), 3.93 (s, 3H), 3.98 (s, 3H), 4.37 (q, J = 7.0 Hz, 2H), 4.49 (m, 1H), 5.56 (s, 1H), 6.61 (s, 1H), 6.90 (dd, J = 2.0, 8.0 Hz, 1H), 7.65 (br. s, 1H), 7.86 (d, J = 8.0 Hz, 1H). ^{13}C NMR (CDCl_3): δ = 14.7, 29.9, 44.7, 56.4, 58.8, 60.6, 62.2, 108.5, 114.4, 115.1, 124.51, 131.2, 131.3, 131.6, 133.1, 142.8, 149.7, 153.4, 155.7, 158.5. HRESIMS calculated for $\text{C}_{20}\text{H}_{22}\text{NO}_5$ $[\text{M}+\text{H}]^+$ 356.1492; found 356.1491.

Compound 14d—Yield 0.031g (83%), colourless oil, R_f = 0.66 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.41 (t, J = 7.2 Hz, 3H), 2.64 (m, 2H), 2.86 (m, 1H), 3.85 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 4.36 (q, J = 7.2 Hz, 2H), 4.52 (m, 1H), 5.53 (s, 1H), 6.59 (s, 1H), 6.92 (dd, J = 2.4, 8.4 Hz, 1H), 7.53 (br. s, 1H), 7.89 (d, J = 8.4 Hz, 1H). ^{13}C NMR

(CDCl₃): δ = 14.8, 29.9, 44.7, 55.5, 56.4, 58.9, 60.6, 61.9, 108.6, 112.4, 113.9 ($\times 2$), 124.2, 131.4, 131.6, 133.3, 142.8, 149.7, 153.3, 157.9, 159.1. HRESIMS calculated for C₂₁H₂₄NO₅ [M+H]⁺ 370.1649; found 370.1652.

Compound 14e—Yield 0.028g (82%), colourless oil, R_f = 0.61 (silica gel, hexanes/EtOAc, 6:4). ¹H NMR (CDCl₃): δ = 1.43 (t, J = 7.1 Hz, 3H), 2.68 (m, 2H), 2.89 (m, 1H), 3.93 (s, 3H), 4.01 (s, 3H), 4.40 (q, J = 7.1 Hz, 2H), 4.55 (m, 1H), 5.60 (s, 1H), 6.69 (s, 1H), 7.30 (dd, J = 7.6, 7.6 Hz, 1H), 7.41 (m, 1H), 7.97 (s, 1H), 8.05 (d, J = 7.6 Hz, 1H). ¹³C NMR (CDCl₃): δ = 14.8, 29.9, 44.7, 56.5, 58.9, 60.6, 61.9, 109.8, 123.7, 126.4, 126.9, 128.2 ($\times 2$), 131.5, 133.8, 138.9, 143.7, 147.7, 153.3, 157.9. HRESIMS calculated for C₂₀H₂₂NO₄ [M+H]⁺ 340.1543; found 340.1549.

Compound 14f—Yield 0.026g (77%), colourless oil, R_f = 0.41 (silica gel, hexanes/EtOAc, 6:4). ¹H NMR (CDCl₃): δ = 1.43 (t, J = 7.0 Hz, 3H), 2.67 (m, 2H), 2.89 (m, 1H), 4.00 (s, 3H), 4.39 (m, 2H), 4.52 (m, 1H), 5.55 (s, 1H), 5.78 (s, 1H), 6.74 (s, 1H), 7.12 (m, 1H), 7.79 (m, 2H). ¹³C NMR (CDCl₃): δ = 14.8, 29.7, 44.6, 58.8, 61.5, 62.1, 112.2, 114.4, 114.9, 115.2, 123.8, 132.7, 133.5, 134.2, 141.0, 149.7, 150.7, 157.8, 162.1. ¹⁹F NMR (CDCl₃): δ = -114.4 (d, J = 360 Hz). HRESIMS calculated for C₁₉H₁₉FNO₄ [M+H]⁺ 344.1220; found 344.1217.

Compound 14g—Yield 0.029 (82%), colourless oil, R_f = 0.39 (silica gel, hexanes/EtOAc, 6:4). ¹H NMR (CDCl₃): δ = 1.43 (t, J = 7.0 Hz, 3H), 2.66 (m, 2H), 2.87 (m, 1H), 3.89 (s, 3H), 4.00 (s, 3H), 4.38 (q, J = 7.0 Hz, 2H), 4.52 (m, 1H), 5.56 (s, 1H), 5.78 (br. s, 1H), 6.68 (s, 1H), 6.97 (dd, J = 1.5, 8.5 Hz, 1H), 7.60 (br. s, 1H), 7.75 (d, J = 8.5 Hz, 2H). ¹³C NMR (CDCl₃): δ = 14.8, 29.8, 44.7, 55.6, 59.0, 61.4, 61.9, 111.3, 112.7, 113.9, 123.7, 130.9, 132.5, 133.2, 140.5, 149.4, 150.0, 158.0, 159.2. HRESIMS calculated for C₂₀H₂₂NO₅ [M+H]⁺ 356.1492; found 356.1497.

Compound 14h—Yield 0.026g (81%), colourless oil, R_f = 0.39 (silica gel, hexanes/EtOAc, 6:4). ¹H NMR (CDCl₃): δ = 1.43 (t, J = 7.0 Hz, 3H), 2.67 (m, 2H), 2.89 (m, 1H), 4.02 (s, 3H), 4.39 (t, J = 7.0 Hz, 2H), 4.54 (m, 1H), 5.59 (s, 1H), 5.79 (s, 1H), 6.75 (s, 1H), 7.31 (m, 2H), 7.43 (dd, J = 7.5, 7.5 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.98 (br. s, 1H). ¹³C NMR (CDCl₃): δ = 14.8, 29.8, 44.7, 59.1, 61.6, 61.9, 112.6, 123.2, 126.5, 127.1, 128.4, 130.5, 132.7, 133.8, 138.3, 141.2, 148.1, 149.3, 157.9. HRESIMS calculated for C₁₉H₂₀NO₄ [M+H]⁺ 326.1314; found 326.1313.

Compound 14i—Yield 0.026g (76%), colourless oil, R_f = 0.41 (silica gel, hexanes/EtOAc, 6:4). ¹H NMR (CDCl₃): δ = 1.43 (t, J = 7.1 Hz, 3H), 2.65 (m, 2H), 2.86 (m, 1H), 3.95 (s, 3H), 4.40 (q, J = 7.1 Hz, 2H), 4.53 (m, 1H), 5.56 (s, 1H), 5.99 (s, 1H), 6.62 (s, 1H), 7.08 (m, 1H), 7.67 (br. s, 1H), 7.96 (dd, J = 5.4, 8.2 Hz, 1H). ¹³C NMR (CDCl₃): δ = 14.7, 29.6, 44.9, 56.7, 58.9, 61.9, 107.5, 114.7, 114.9, 124.5, 127.1, 133.8, 135.1, 139.9, 147.2, 149.5, 157.9, 160.8, 162.8. HRESIMS calculated for C₁₉H₁₉FNO₄ [M+H]⁺ 344.1220; found 344.1227.

Compound 14j—Yield 0.030g (81%), colourless oil, R_f = 0.38 (silica gel, hexanes/EtOAc, 6:4). ¹H NMR (CDCl₃): δ = 1.42 (m, 3H), 2.64 (m, 2H), 2.85 (m, 1H), 3.94 (s, 3H), 4.38 (m, 2H), 4.52 (m, 1H), 5.48 (s, 1H), 5.92 (s, 1H), 6.00 (s, 1H), 6.02 (s, 1H), 6.57 (s, 1H), 7.53 (br. s, 2H). ¹³C NMR (CDCl₃): δ = 14.7, 29.6, 44.8, 56.6, 58.7 ($\times 2$), 61.9, 101.2 ($\times 2$), 104.5, 106.8, 126.9, 133.1, 134.1, 139.3, 141.5, 146.5, 147.1, 147.5, 157.9. HRESIMS calculated for C₂₀H₂₀NO₆ [M+H]⁺ 370.1285; found 370.1289.

Compound 14k—Yield 0.027g (77%), colourless oil, R_f = 0.39 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.44 (t, J = 7.0 Hz, 3H), 2.65 (m, 2H), 2.85 (m, 1H), 3.87 (s, 3H), 3.94 (s, 3H), 4.40 (q, J = 7.0 Hz, 2H), 4.53 (m, 1H), 5.58 (s, 1H), 5.94 (s, 1H), 6.57 (s, 1H), 6.95 (dd, J = 2.0, 8.3 Hz, 1H), 7.55 (br. s, 1H), 7.92 (d, J = 8.3 Hz, 1H). ^{13}C NMR (CDCl_3): δ = 14.8, 29.7, 44.8, 55.5, 56.5, 59.0, 61.8, 106.8, 112.4, 113.6, 124.2, 126.9 ($\times 2$), 131.9, 133.6, 139.4, 147.1, 149.1, 157.9, 158.7. HRESIMS calculated for $\text{C}_{20}\text{H}_{22}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 356.1492; found 356.1491.

Compound 14l—Yield 0.030g (79%), colourless oil, R_f = 0.36 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.43 (m, 3H), 2.65 (m, 2H), 2.88 (m, 1H), 3.95 (s, 3H), 3.96 (s, 3H), 4.00 (s, 3H), 4.41 (m, 2H), 4.52 (m, 1H), 5.51 (s, 1H), 5.92 (s, 1H), 6.57 (s, 1H), 7.59 (br. s, 2H). ^{13}C NMR (CDCl_3): δ = 14.9, 29.8, 44.9, 56.07, 56.14, 56.7, 58.9, 61.9, 106.7 ($\times 2$), 110.4, 126.9, 131.9, 134.1, 139.3, 139.9, 147.2, 147.9, 149.1, 158.0. HRESIMS calculated for $\text{C}_{21}\text{H}_{24}\text{NO}_6$ [$\text{M} + \text{H}$] $^+$ 386.1598; found 386.1597.

Compound 14m—Yield 0.040g (93%), colourless oil, R_f = 0.61 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.10 (m, 3H), 2.65 (m, 1H), 2.90 (m, 1H), 3.79 (m, 2H), 3.89 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 4.06 (m, 2H), 5.40 (s, 1H), 6.92 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H). ^{13}C NMR (CDCl_3): δ = 14.3, 22.7, 45.5, 56.2, 60.5, 60.7, 60.8, 61.1, 61.2, 61.4, 76.8, 112.6, 118.1, 122.5, 126.2, 132.6, 137.7, 146.3, 146.6, 147.3, 150.3, 151.7, 157.1. HRESIMS calculated for $\text{C}_{23}\text{H}_{28}\text{NO}_7$ [$\text{M} + \text{H}$] $^+$ 430.1860; found 430.1861.

Compound 14n—Yield 0.036g (91%), colourless oil, R_f = 0.62 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.43 (t, J = 7.0 Hz, 3H), 2.63 (m, 2H), 2.99 (m, 1H), 3.87 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 4.03 (s, 3H), 4.40 (q, J = 7.0 Hz, 2H), 4.55 (m, 1H), 5.53 (s, 1H), 6.93 (dd, J = 2.5, 8.5 Hz, 1H), 7.53 (br. s, 1H), 7.83 (d, J = 8.5 Hz, 1H). ^{13}C NMR (CDCl_3): δ = 14.8, 24.6, 44.3, 55.6, 59.2, 60.9, 61.3, 61.8, 62.0, 112.2, 113.9, 123.5, 124.8, 126.8, 131.8, 136.6, 146.0, 147.5, 149.0, 149.2, 157.8, 158.6. HRESIMS calculated for $\text{C}_{22}\text{H}_{26}\text{NO}_6$ [$\text{M} + \text{H}$] $^+$ 400.1755; found 400.1757.

Compound 16a—Yield 0.019g (46%), colourless oil, R_f = 0.46 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.15 (t, J = 7.5 Hz, 3H), 3.20 (m, 2H), 3.43 (m, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H), 4.05 (m, 2H), 5.03 (br. s, 1H), 6.95 (dd, J = 2.5, 8.0 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H). ^{13}C NMR (CDCl_3): δ = 14.6, 24.5, 29.7, 41.6, 55.6, 60.4, 60.5, 60.8, 61.2, 109.1 ($\times 2$), 120.0, 124.1 ($\times 2$), 127.3, 131.3, 134.7, 136.4, 147.3, 152.2, 156.7, 160.1. HRESIMS calculated for $\text{C}_{22}\text{H}_{26}\text{NO}_7$ [$\text{M} + \text{H}$] $^+$ 416.1631; found 416.1632.

Compound 16b—Yield 0.019g (53%), colourless oil, R_f = 0.46 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.21 (m, 3H), 3.22 (m, 2H), 3.50 (m, 2H), 3.97 (s, 6H), 4.11 (q, J = 7.1 Hz, 2H), 6.56 (s, 1H), 7.31 (m, 2H), 7.50 (m, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.87 (d, J = 7.4 Hz, 1H). ^{13}C NMR (CDCl_3): δ = 14.67, 31.6, 41.7, 56.2, 60.4, 60.7, 113.4, 123.6, 123.9, 124.6, 128.77, 134.5, 135.4, 137.9, 141.9, 143.7, 156.8, 158.7. HRESIMS calculated for $\text{C}_{20}\text{H}_{22}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 356.1492; found 356.1491.

Compound 19—Yield 0.035g (91%), colourless oil, R_f = 0.1 (silica gel, hexanes/EtOAc, 6:4). ^1H NMR (CDCl_3): δ = 1.41 (s, 9H), 3.23 (m, 2H), 3.44 (m, 2H), 3.98 (s, 3H), 4.01 (s, 3H), 4.77 (br. s, 1H), 6.64 (s, 1H), 7.48 (d, J = 4.5 Hz, 1H), 8.70 (d, J = 4.5 Hz, 1H), 9.16 (s, 1H). ^{13}C NMR (CDCl_3): δ = 28.2, 32.1, 41.1, 56.0, 60.5, 114.5, 116.9, 124.1, 135.6, 139.6, 141.5, 143.9, 144.9, 151.5, 156.2, 159.1. HRESIMS calculated for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_5$ [$\text{M} + \text{H}$] $^+$ 385.1758; found 385.1758.

Synthesis of compound 17 - procedure for deprotection and oxidation to azafluoranthenes

To a solution of azafluoranthene **12** (0.038 g, 0.1 mmol) in dry DMSO (1 mL) was added DBU (0.152 g, 1 mmol) under N₂ and the reaction mixture was purged with oxygen (balloon). The reaction mixture was stirred at 40 °C for 8h. Water (5 mL) was added to the reaction mixture and extracted with dichloromethane (5 mL). The organic layer was washed sequentially with water (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel in 30% ethyl acetate/hexanes to yield **17** (79%). Similar procedures were used to synthesize compounds **1** (76%) and **3** (77%).

Compound 17—Yield 0.030g (79%), pale yellow oil, R_f = 0.3 (silica gel, hexanes/EtOAc, 6:4). ¹H NMR (CDCl₃): δ= 4.05 (s, 3H), 4.11 (s, 3H), 6.10 (s, 2H), 6.96 (s, 1H), 7.37 (d, J =6.0 Hz, 1H), 7.53 (s, 1H), 7.57 (s, 1H), 8.55 (d, J =6.0 Hz, 1H). ¹³C NMR (CDCl₃): δ= 56.3, 61.3, 101.7, 103.2, 104.1, 106.0, 116.5, 123.1, 126.1, 130.1, 133.0, 133.9, 145.4, 147.0, 148.0, 149.1, 158.7, 159.0. HRESIMS calculated for C₁₈H₁₄NO₄ [M+H]⁺ 308.0917; found 308.0918.

Compound 1—Yield 0.025g (76%), colourless oil, R_f = 0.32 (silica gel, hexanes/EtOAc, 6:4). ¹H NMR (CDCl₃): δ= 3.96 (s, 3H), 4.07 (s, 3H), 4.13 (s, 3H), 4.15 (s, 3H), 6.99 (dd, J =2.5, 8.5 Hz, 1H), 7.66 (d, J =6.0 Hz, 1H), 7.70 (d, J =2.5 Hz, 1H), 7.85 (d, J =8.5 Hz, 1H), 8.62 (d, J =6.0 Hz, 1H). ¹³C NMR (CDCl₃): δ= 55.7, 61.45, 61.49, 62.1, 107.3, 113.8, 116.0, 122.2, 124.1, 124.6, 126.3, 131.1, 140.3, 144.6, 148.4, 149.9, 150.6, 159.0, 159.8. HRESIMS calculated for C₁₉H₁₈NO₄ [M+H]⁺ 324.1230; for 324.1231.

Compound 3—Yield 0.021g (77%), colourless oil, R_f = 0.34 (silica gel, hexanes/EtOAc, 6:4). ¹H NMR (CDCl₃): δ= 4.05 (s, 3H), 4.12 (s, 3H), 7.02 (s, 1H), 7.45 (m, 3H), 8.04 (m, 1H), 8.10 (m, 1H), 8.60 (dd, J =5.0, 5.0 Hz, 1H). ¹³C NMR (CDCl₃): δ=56.4, 61.4, 104.7, 117.1, 121.9, 123.3, 124.8, 126.6, 128.4, 129.8, 131.1, 138.2, 139.2, 145.7, 147.8, 159.1. HRESIMS calculated for C₁₇H₁₄NO₂ [M+H]⁺ 264.1019; found 264.1020.

Synthesis of Compound 20

Compound **19** (44mg, 0.1 mmol), which was synthesized following the general procedure for direct arylation, was dissolved in DCM: TFA (1:1, 1 mL) and stirred at room temperature for 3 hours. Solvents were evaporated under reduced pressure and the residue was re dissolved in DCM (5 mL). The DCM layer was washed with 5% NaHCO₃ solution (5 mL), water (5 mL), brine (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluted in neat ethyl acetate to give **20** (31 mg, 90%).

Compound 20—Yield 0.030g (90%), colourless oil, R_f = 0.51 (silica gel, 100% EtOAc, 6:4). ¹H NMR (CDCl₃): δ= 2.83 (t, J =8.5 Hz, 2H), 3.93 (s, 3H), 3.99 (s, 3H), 4.27 (t, J =8.5 Hz, 2H), 6.62 (s, 1H), 7.69 (d, J =5.0 Hz, 1H), 8.64 (d, J = 5.0 Hz, 1H), 9.11 (s, 1H). ¹³C NMR (CDCl₃): δ= 22.6, 50.8, 56.4, 60.8, 110.8, 116.6, 121.2, 128.4, 129.9, 136.3, 143.5, 144.33, 145.0, 149.7, 157.9, 165.0. HRESIMS calculated for C₁₆H₁₅N₂O₂ [M+H]⁺ 267.1128; found 267.1130.

Synthesis of Compound 21

Compound **20** (0.017 g, 0.05 mmol) was dissolved in DCM (0.5 mL) and DBU (0.015 g, 0.1 mmol) was added to the reaction mixture at rt. The resulting dark brown solution was stirred at rt under open air for 4h. Water (5 mL) was added to the reaction mixture and extracted with DCM (5 mL). The DCM layer was washed with water, brine, dried on Na₂SO₄, filtered

and concentrated in vacuo. The residue was purified by chromatography on silica gel in 50% ethyl acetate/hexanes to afford **21** (0.014g, 83%).

Compound 21—Yield 0.014g (83%), pale yellow oil, R_f = 0.52 (silica gel, 100% EtOAc). ^1H NMR (CDCl_3): δ = 4.09 (s, 3H), 4.18 (s, 3H), 7.10 (s, 1H), 7.57 (d, J =5.5 Hz, 1H), 8.10 (dd, J = 1.0, 5.0 Hz, 1H), 8.71 (d, J =5.5 Hz, 1H), 8.73 (d, J =5.0 Hz, 1H), 9.28 (s, 1H). ^{13}C NMR (CDCl_3): δ = 56.6, 61.7, 105.3, 116.4, 116.6, 118.8, 123.8, 124.2, 131.2, 132.8, 145.3, 146.2, 148.5, 149.8, 156.6, 159.3. HRESIMS calculated for $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 265.0977; found 265.0978.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1. $R_1 = \text{OMe}$, $R_2 = \text{H}$, $R_3 = \text{OMe}$, $R_4 = \text{H}$
2. $R_1 = R_2 = R_3 = \text{OMe}$, $R_4 = \text{H}$
3. $R_1 = R_2 = R_3 = R_4 = \text{H}$

Figure 1.

Structures of the azafluoranthene alkaloids rufescine (1), imeluteine (2) and triclisine (3) and the aporphine alkaloid nantenine (4)

Figure 2.
Retrosynthetic analysis for azafluoranthene synthesis

Scheme 1.
Synthesis of biaryl coupling substrate **11**

Scheme 2.
Alternative coupling approach

Scheme 3. Synthesis of nantenine analog **17**, rufescine (**1**) and triclisine (**3**)

Scheme 4.
Synthesis of "azafluoranthene-like" alkaloid **21**

Table 1

Optimization of direct arylation on **11**

<div style="text-align: center;"> Ligands A (PhDavePhos) B (DavePhos) C </div>				
Entry	Ligand	Base	Solvent	Yield (%) ^a
1	A	K ₂ CO ₃	DMA	0
2	B	K ₂ CO ₃	DMA	26
3	C	K ₂ CO ₃	DMA	31
4	A	Cs ₂ CO ₃	DMSO	0
5	B	Cs ₂ CO ₃	DMSO	0
6	C	Cs ₂ CO ₃	DMSO	38
7	A	K ₂ CO ₃	DMSO	12
8	B	K ₂ CO ₃	DMSO	41
9 ^b	C	K ₂ CO ₃	DMSO	91

^a Isolated yields. Reactions run on a 0.1 mmol scale.^b Under thermal conditions, the yield of this combination was 82% after 24h.

Table 2

Direct arylation with other substrates

Cmpd	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Yield (%)
14a	Me	Me	H	H	OMe	OMe	89
14b	Me	Me	H	H	F	H	86
14c	Me	Me	H	H	OH	H	81
14d	Me	Me	H	H	OMe	H	83
14e	Me	Me	H	H	H	H	82
14f	Me	H	H	H	F	H	77
14g	Me	H	H	H	OMe	H	82
14h	Me	H	H	H	H	H	81
14i	H	Me	H	H	F	H	76
14j	H	Me	H	H	O	OCH ₂	81
14k	H	Me	H	H	OMe	H	77
14l	H	Me	H	H	OMe	OMe	79
14m	Me	Me	OMe	OMe	OMe	H	93
14n	Me	Me	OMe	H	OMe	H	91