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# Collective Total Synthesis of 4-Azafluorenone Alkaloids

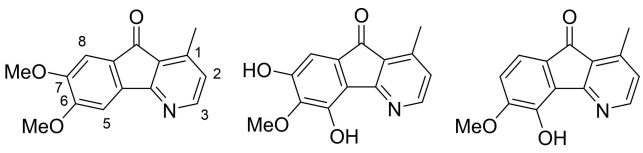
Ilya A. P. Jourjine[a] and Franz Bracher*[a]

4-Azafluorenones are typically obtained by acid-mediated cyclization of 2-arylnicotinates. However, this approach fails to give 5-oxygenated 4-azafluorenones due to lactonization of 2-(2-alkoxy)phenylnicotinate intermediates. Herein, we report two modifications of established approaches to 4-azafluorenone synthesis that, either in combination or by themselves, enable the flexible preparation of 4-azafluorenones with diverse oxygenation patterns in the benzenoid ring. Undesired lactonization was circumvented *via tert*-butyl hydroperoxide (TBHP)-mediated radical cyclization of 2-aryl-3-(hydroxymethyl)pyridines. In the absence of suitable protecting groups for phenolic intermediates, bromide substituents were regioselectively introduced as latent hydroxy groups and later converted under palladium catalysis. We present the first total syntheses of five 4-azafluorenone alkaloids muniranine, darienine, 5,8-dimethoxy-7-hydroxyonychine, 5,6,7,8-tetramethoxyonychine, and 6,8-dihydroxy-7-methoxyonychine in addition to new total syntheses of six 4-azafluorenone alkaloids and one related pyridocoumarin alkaloid.

## Introduction

4-Azafluorenone alkaloids isolated from various plants like those belonging to the Annonaceae family comprise a small group of tricyclic fused heterocycles speculated to be biosynthetically derived from aporphine precursors.[1] 4-Azafluorenones and their derivatives, both naturally occurring and synthetic, have emerged as compounds of profound pharmacological interest on account to their diverse biological properties that make them attractive scaffolds for drug development, such as antibacterial activity against multiple strains including *Bacillus subtilis*,[2] as well as antifungal,[3] antiprotozoal,[4] herbicidal[5] and antiproliferative qualities.[6] Furthermore, they have been reported for their role in enzyme activity regulation such as exhibiting adenosine A2 receptor binding and phosphodiesterase inhibition,[7] thrombin inhibition[8] and calcium antagonistic activity.[9] Moreover, natural 4-azafluorenones like polyfothine (**1**), cyathocaline (**2**) and isoursuline (**3**; sometimes referred to as oxylopine), display DNA damaging,[6c] DNA modifying[10] and antimalarial[11] activity, respectively (Scheme 1).

Azafluorenones are also used in organic light-transmitting devices (OLED) as electron-transporting host materials.[12] The isomeric 2-azafluorenones specifically have been shown to inhibit phosphatidyl-inositol specific phospholipase C activation,[13] and were demonstrated to be effective photoactivatable fluorescent probes for lipid droplet-specific live cell imaging.[14]




**Scheme 1.** Representative examples of pharmacologically active azafluorenone alkaloids: polyfothine (**1**), cyathocaline (**2**) and isoursuline (**3**).

The simplest member of the 4-azafluorenone alkaloids is onychine (**4**), which was first isolated in 1976 from *Onychopetalum amazonicum* (Annonaceae).[15] Its initially published structure was reassigned to be 4-aza-1-methylfluoren-9-one by independent synthesis in 1979 after an initial erroneous report.[16] Noticeably, onychine (**4**) was first synthesized as an intermediate for the total synthesis of the diazafluoranthene alkaloid eupolauridine even before it was identified as a natural product.[17] The most pervasive approaches to onychine (**4**) synthesis concern themselves with the construction of the 1-methyl-4-azafluorene framework by means of catalytic dehydrocyclization of 2-aryl-3-methylpyridines,[18] Pummerer cycloaddition cascade,[19] hetero-Diels-Alder cycloaddition[20] and intramolecular aza-Wittig reaction[21] followed by oxidation (Scheme 2, I). The most prominent methods feature 2-aryl-4-methylnicotinate esters[22] or corresponding carboxylic acids[8,23] or acyl chlorides[24] as key intermediates, which are then subjected to intramolecular Friedel-Crafts-type acylation in strongly acidic media or using zeolites (Scheme 2, II).[25] Consequently, the development of new synthetic methods to access appropriate 2-arylnicotinate esters has been the topic of extensive research. Published methods include Suzuki-Miyaura coupling,[22a] condensation of 1,5-dicarbonyl compounds with hydroxylamine hydrochloride,[22b,c,24] C–H arylation of 2-halopyridine *N*-oxides with Grignard reagents,[22d] multicomponent

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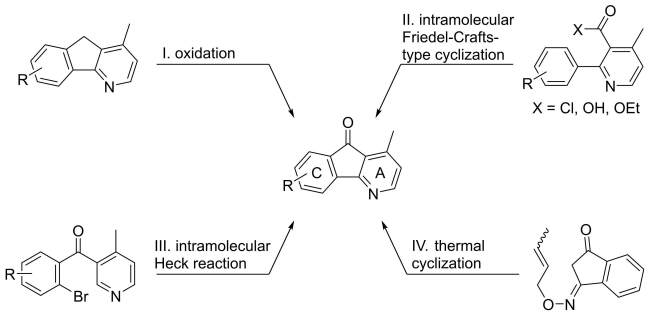


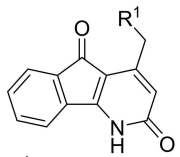

**Scheme 2.** Selected general approaches to the synthesis of onychine (**4**; R=H) and related 4-azafluorenone alkaloids.

tandem reaction using a Blaise intermediate,[26] $FeCl_3$-mediated condensation of α-phenylenamino esters and enones[22f] and reaction of azatrienes with α,β-unsaturated aldehydes as their key steps.[27] Although no example for onychine (**4**) synthesis was provided, *tert*-butyl hydroperoxide (TBHP) has been successfully employed in the radical cyclization of 3-hydroxymethyl-2-phenylpyridine, 2-(pyridinyl)benzylalcohols[28] and nicotinaldehydes[29] for the synthesis of various 1-, 2-, 3- and 4-azafluorenones, respectively. Further noteworthy synthetic strategies for onychine (**4**) synthesis include biaryl linkage of azabenzophenones *via* Pd-catalyzed intramolecular Heck reaction[30] (Scheme 2, III), application of the aza-Morita-Baylis-Hillman reaction,[31] as well as directed *ortho*-metalation of 2-(4-chloro-2-pyridyl)benzamide and subsequent methylation *via* Suzuki-Miyaura cross-coupling.[32]

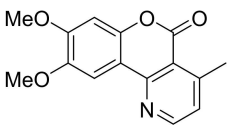
Finally, thermal cyclization of both indanoneoxime *O*-crotyl ethers[33] (Scheme 2, IV) and indanone *N*-propargyl enamines have been reported,[34] although plausibly affording isomeric mixtures of 4-azafluorenones with respect to the position of the methyl group.

To date, 30 natural congeners of onychine (**4**) have been isolated and identified, which differ in position and degree of hydroxy and/or methoxy substituents (Scheme 3).[1,2d,6c,11,15,23,35] Total synthesis of most ring C monosubstituted derivatives,[36] including our group's regioselective synthesis of 6-methoxyonychine,[37] and a select few disubstituted derivatives[30a,35d] using the methods described above have been reported. Still, there are no reports on the total synthesis for derivatives with more complex substitution patterns. Simple protocols reported for the synthesis of onychine (**4**) derivatives containing phenolic hydroxy groups in ring C feature regioselective *O*-demethylation of single methoxy groups.[35b,36] Phenolic derivatives that are not as conveniently accessible require a different approach, however, as demonstrated by Koyama's total synthesis of ursuline (**5**) and isoursuline (**3**)[35d] and Achenbach's synthesis of 2-methoxyonychine alkaloids containing phenolic hydroxy groups,[22e] respectively. While many approaches appear elegant in their final steps, they are often limited by the complexity of the starting materials and require harsh reaction conditions. In summary, a flexible protocol for the synthesis of ring C hydroxylated 4-azafluorenones is long-needed. Susceptibility of nicotinate esters with 2-(2-methoxy)phenyl residues to lactonization in strongly acidic media employed for Friedel-Crafts acylation further restricts accessibility of 4-azafluorenone alkaloids furnishing alkoxy residues at C-5 with many known procedures (Scheme 4).[23,38] Unpublished experiments of our group with 2-(2-benzyloxy)phenyl residues suggest that this behavior extends to alkoxy residues in general. Related cyclizations of 2′-methoxybiphenyl-2-carboxylates or esters with $SOCl_2$[39] and $BBr_3$[40] respectively to furnish lactones have also been reported. Notably, one lactone of this type, polynemoraline C (**14**) (Scheme 3) has been identified as a natural product from *Polyalthia nemoralis* (Annonaceae).[41]

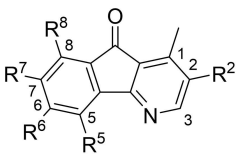
Herein, we report a general procedure for the synthesis of phenolic 4-azafluorenone alkaloids building on a previously



$R^1$ = H **Dielsine**
$R^1$ = OH **Dielsinol**



**Polynemoraline C** (**14**)



| | |
|---|---|
| $R^2 = R^5 = R^8$ = H; $R^6 = R^7$ = OMe **Polyfothine** (**1**) | $R^2 = R^5 = R^6$ = H; $R^7$ = OH; $R^8$ = OMe **Macondine** |
| $R^2 = R^8$ = H; $R^5 = R^7$ = OH; $R^6$ = OMe **Cyathocaline** (**2**) | $R^2 = R^5 = R^8$ = H; $R^6$ = OMe; $R^7$ = OH **Isooncodine** |
| $R^2 = R^7 = R^8$ = H; $R^5$ = OH; $R^6$ = OMe **Isoursuline** (**3**) | $R^2 = R^5$ = H; $R^6 = R^7$ = OH; $R^8$ = OMe **Penduline** |
| $R^2 = R^5 = R^6 = R^7 = R^8$ = H **Onychine** (**4**) | $R^2 = R^7$ = H; $R^5 = R^8$ = OH; $R^6$ = OMe |
| $R^2 = R^7 = R^8$ = H; $R^5$ = OMe; $R^6$ = OH **Ursuline** (**5**) | $R^2 = R^5 = R^7 = R^8$ =H; $R^6$ = OMe |
| $R^2$ = H; $R^5 = R^7 = R^8$ = OMe; $R^6$ = OH **Muniranine** (**6**) | $R^2 = R^6 = R^7 = R^8$ =H; $R^5$ = OH |
| $R^2 = R^8$ = H; $R^5 = R^6$ = OMe; $R^7$ = OH **Darienine** (**7**) | $R^2 = R^5 = R^7 = R^8$ =H; $R^6$ = OH |
| $R^2 = R^6$ = H; $R^5 = R^8$ = OMe; $R^7$ = OH (**8**) | $R^2 = R^5 = R^6 = R^8$ =H; $R^7$ = OH |
| $R^2$ = H; $R^5 = R^6 = R^7 = R^8$ = OMe (**9**) | $R^2 = R^5 = R^6 = R^7$ =H; $R^8$ = OH |
| $R^2 = R^8$ = H; $R^5$ = OH; $R^6 = R^7$ = OMe (**10**) | $R^2$ = OH; $R^5 = R^6 = R^7 = R^8$ = H |
| $R^2 = R^5 = R^6 = R^8$ =H; $R^7$ = OMe (**11**) | $R^2 = R^7$ = OH; $R^5 = R^6 = R^8$ = H |
| $R^2 = R^5 = R^8$ = H; $R^6$ = OH; $R^7$ = OMe **Oncodine** (**12**) | $R^2$ = OMe; $R^5 = R^6 = R^8$ = H; $R^7$ = OH |
| $R^2 = R^5$ = H; $R^6 = R^8$ = OH; $R^7$ = OMe (**13**) | $R^2 = R^6$ = OMe; $R^5 = R^8$ = H; $R^7$ = OH |
| $R^2 = R^7$ = H; $R^5 = R^8$ = OMe; $R^6$ = OH **Kinabaline** | $R^2 = R^8$ = OMe; $R^5 = R^6$ = H, $R^7$ =OH |

**Scheme 3.** Known 4-azafluorenone alkaloids and related natural products. *Note:* The structure of dielsine is questionable.[42]

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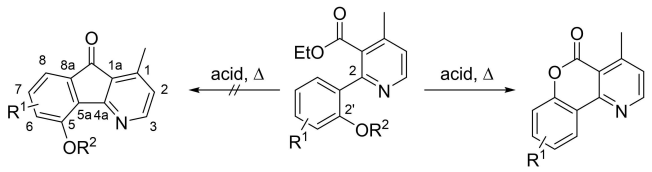
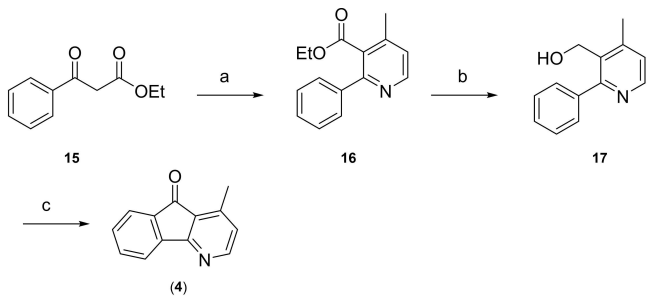



**Scheme 4.** Lactonization of 2-(2-alkoxyphenyl)-substituted nicotinic acid esters.

published synthesis of ours for onychine (**4**)[22b] that employs a) TBHP-mediated radical cyclization of 3-pyridinemethanol-type intermediates to circumvent lactonization of nicotinate ester intermediates with 2-(2-alkoxy)phenyl residues, and b) bromide substituents as latent hydroxy groups. With these two methods, either alone or in combination, we circumvented the undesired lactonization of 5-methoxy/hydroxyazafluorenone precursors and the lack of phenol protective groups stable to the diverse reaction conditions of the synthesis route presented herein. Furthermore, in some cases, brominated benzaldehydes (as precursors of 2-arylnicotinates) are easier accessible than the corresponding hydroxybenzaldehydes.

## Results and Discussion

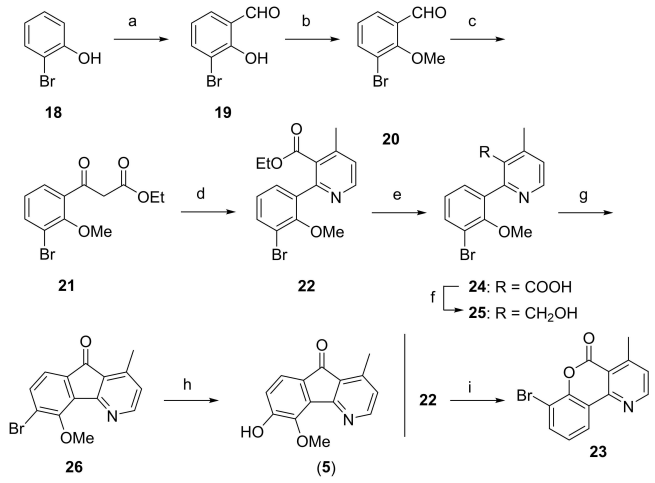
We commenced our investigations with onychine (**4**) as the model synthesis route (Scheme 5). Commercially available ethyl 3-oxo-3-phenylpropionate (**15**) was reacted with catalytic amounts of benzyltrimethylammonium hydroxide and crotonaldehyde in a base-catalyzed Michael-Addition and the *in situ* generated intermediate was treated with hydroxylammonium chloride to give 2-phenylnicotinic acid ester **16** in a yield of 40%.[22b] In search for an alternative, non-acid promoted intramolecular cyclization, we opted for a TBHP-mediated radical cyclization protocol utilizing hydroxymethylated phenylpyridines which had been employed by Laha[28] for the synthesis of azafluorenones, and by us for structurally related fluorenones starting from 2-arylbenzylamines.[43] For this purpose, the nicotinic acid ester **16** was first reduced with LAH[44] to give pyridinemethanol **17**, and subsequent cyclization with TBHP in nonane ($TBHP_{non}$) gave onychine (**4**) with a yield of 55%. The reaction conditions employed for the TBHP-mediated radical cyclization (Scheme 5, reaction c)) represent the best result achieved after attempts at reaction optimization in aforementioned work on fluorenone synthesis.[43] In addition, the commonly employed additive *tert*-butyl ammonium iodide for TBHP-mediated acyl radical reactions[45] was also tested, however, this promoted the generation of more side-products (detected by TLC control).




**Scheme 5.** Total synthesis of onychine (**4**). Conditions: a) Benzyltrimethylammonium hydroxide (catalytic), crotonaldehyde, then hydroxylammonium chloride, 1,4-dioxane/AcOH (1:1), rt – 100 °C, 1 h, 40%; b) LAH, THF, rt, 16 h, 65%; c) $TBHP_{non}$, 1,2-DCE, 100 °C, 18 h, 55%. Total yield: 14% over three steps.

Although in comparison with the more commonly employed Friedel-Crafts cyclization in strongly acidic media (PPA) an additional step is required to generate the pyridinemethanol from the nicotinic acid ester, we expected to avoid lactonization with esters furnishing a 2-(2-alkoxyphenyl) residue, as we had been successful in synthesizing 5-oxygenated fluorenones using a related method in previous research.[43] To put this theory to the test, we proceeded with the synthesis of ursuline[35d] (**5**), bearing a methoxy group at C-5 and a free hydroxy group at C-6 (Scheme 6). In unpublished research of ours, we found that free hydroxy groups favored formation of unwanted side-products during construction of the pyridine ring and would most likely cause similar issues during TBHP-cyclization.[43] Moreover, conventional phenol protecting groups like TBS or SEM were not stable to the conditions of at least one of the steps in the synthesis route. Therefore, starting material bearing a bromide-substituent acting as a latent hydroxy group was employed.

2-Bromophenol (**18**) was regioselectively *ortho*-formylated[46] and the resulting crude aldehyde **19** *O*-methylated to give aldehyde **20** in two steps with a yield of 62%. This aldehyde was then directly converted into β-ketoester **21** with ethyl diazoacetate under $SnCl_2$ catalysis[47] with a yield of 35%. Keto-



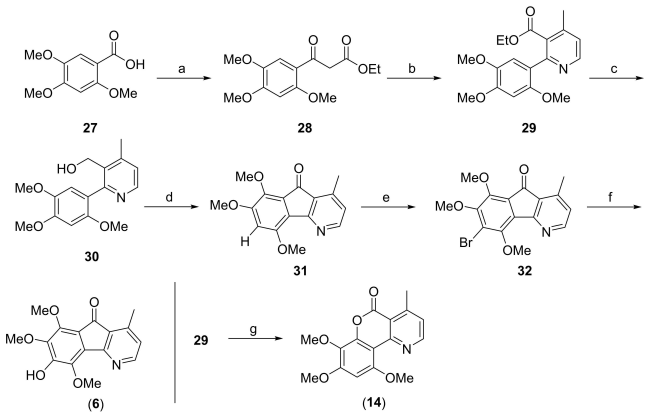

**Scheme 6.** Total synthesis of ursuline (**5**).[35d] Conditions: a) $MgCl_2$, paraformaldehyde, $NEt_3$, THF, 100 °C, 18 h; b) $K_2CO_3$, $CH_3I$, DMF, rt, 16 h, 62% over two steps; c) $SnCl_2$ (catalytic), ethyl diazoacetate, DCM, rt, 1 h, 35%; d) benzyltrimethylammonium hydroxide (catalytic), crotonaldehyde, hydroxylammonium chloride, 1,4-dioxane/AcOH (1:1), rt – 100 °C, 1 h, 34%; e) KOH, $H_2O$/EtOH, 100 °C, 4 h, 82%; f) $BH_3 \cdot SMe_2$, THF, 39%; g) $TBHP_{non}$, 1,2-DCE, 100 °C, 18 h, 23%; h) $Pd_2(dba)_3$ (catalytic), KOH, $Me_4$*t*BuXPhos (catalytic), 1,4-dioxane/$H_2O$ (1:1), 18 h, 100 °C, 70%; i) PPA, 1.5 h, 150 °C, 59%.

enol tautomerism between β-ketoesters and their two enol forms result in complex NMR spectra.[48] The β-ketoester **21** was reacted with crotonaldehyde and hydroxylammonium chloride in the manner described above to give nicotinic acid ester **22** in 34% overall yield. To illustrate the problem with undesired lactonization under acidic conditions, we reacted ester **22** with PPA, which furnished, as expected, the lactone **23** with a yield of 59% instead of the desired azafluorenone **26**. The previously employed one-step ester to primary alcohol reduction with LAH (Scheme 5) ran risk of reductive removal of the bromide substituent, so a more suitable two-step reduction was performed to avoid the use of complex metal hydrides. Carboxylic acid **24** was furnished *via* alkaline ester hydrolysis of **22** in 82% yield, which then gave pyridinemethanol **25** by means of reduction with $BH_3 \cdot SMe_2$[49] with a yield of 39%. Subsequent TBHP-mediated radical cyclization of pyridinemethanol **25** provided azafluorenone **26**, albeit with a poor yield of 23%. Finally, the bromide residue was converted into a free phenol moiety under Pd-catalysis.[50] The method published by Buchwald et al. gave the natural product ursuline (**5**) in a high yield of 70% without any reaction optimization.

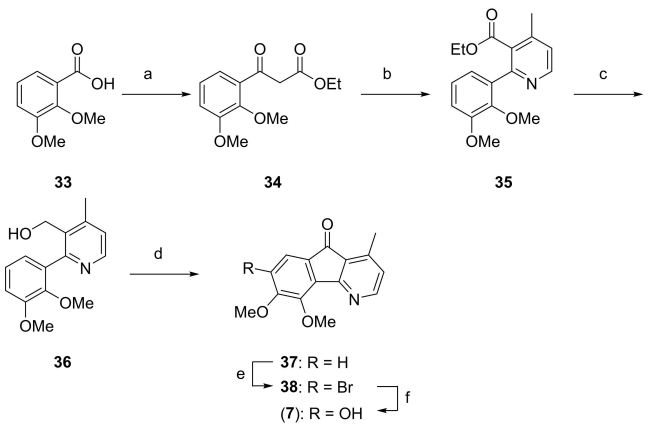
The synthesis of muniranine (**6**), an alkaloid containing a hexasubstituted benzene ring, commenced with the conversion of commercially available 2,4,5-trimethoxybenzoic acid (**27**) to the acyl chloride with $SOCl_2$. β-Ketoester synthesis under published conditions[51] furnished the product **28** by reacting the *in-situ* generated acyl chloride directly with ethyl potassium malonate, $MgCl_2$ and $NEt_3$ (Scheme 7). Preparation of nicotinic acid ester **29** performed unexpectedly sluggishly, and co-eluting side-products made purification by flash column chromatography difficult. As such, the crude ester **29** was used in the following step directly. Reaction with PPA gave the lactone-type natural product polynemoraline C (**14**) with a poor yield of 4% (over two steps from **28**). Meanwhile, LAH reduction of ester **29** gave pyridinemethanol **30**, which was then cyclized to furnish azafluorenone **31** by treatment with TBHP with a yield of 9% over two steps. The 6-hydroxy group was introduced by late-stage functionalization. This was accomplished *via* regioselective bromination at C-6 with NBS and subsequent bromide-to-phenol conversion of bromoarene **32** gave muniranine (**6**) (63% yield) in a total of six steps.

The synthesis of darienine[52] (**7**) followed the same rationale, whereby pyridinemethanol **36** was prepared starting from 2,3-dimethoxybenzoic acid (**33**) over three steps in acceptable yields, comprising the synthesis of β-ketoester **34** and nicotinic acid ester **35**, followed by LAH reduction of the ester group (Scheme 8). Subsequent TBHP-mediated cyclization of pyridinemethanol **36** afforded azafluorenone **37** in a yield of 24%. Late-stage functionalization *via* regioselective bromination at C-6 and subsequent Pd-catalyzed bromide-to-phenol conversion of azafluorenone **38** gave the natural product darienine (**7**) in a yield of 32%.

This late-stage functionalization strategy was also employed for the total synthesis of 7-hydroxy-5,8-dimethoxyonychine[53] (**8**) (Scheme 9). Commercially available carboxylic acid **39** was converted to pyridinemethanol **42** in three steps. TBHP-mediated cyclization thereof afforded azafluorenone **43** with a yield of 21%. Subsequent ring bromination with NBS gave a single regioisomer in a yield of 91%. Determining whether the C-6 or C-7 brominated isomer had formed, however, proved difficult. As such, the carbonyl group of the bromination product **44** was reduced with $NaBH_4$[54] to give azafluorenol **45** to facilitate elucidation of the bromine substituent's position *via* 2D NMR spectroscopy. A HMBC experiment gave a $^3J$-correlation of H-9 to one of two methoxy carbon signals. This methoxy carbon signal in turn showed a $^3J$-correlation to the H atom signal of the phenyl ring, which allowed us to confirm both compounds **44** and **45** as the C-7 brominated regioisomers. Finally, bromoazafluorenone **44** was converted to the hydroxylated natural product **8** in 59% yield.




**Scheme 7.** Total synthesis of muniranine[2d] (**6**) and polynemoraline C[41] (**14**). Conditions: a) $SOCl_2$, ethyl potassium malonate, $MgCl_2$, $NEt_3$, EtOAc, 66%; b) benzyltrimethylammonium hydroxide (catalytic), crotonaldehyde, hydroxylammonium chloride, 1,4-dioxane/AcOH (1:1), rt – 100 °C, 1 h; c) LAH, THF, 18 h, 9% over two steps; d) $TBHP_{non}$, 1,2-DCE, 100 °C, 18 h, 16%; e) NBS, $H_2SO_4$, 50 °C, 1.5 h, 65%; f) $Pd_2(dba)_3$ (catalytic), KOH, $Me_4$*t*BuXPhos (catalytic), 1,4-dioxane/$H_2O$ (1:1), 18 h, 100 °C, 63%; g) PPA, 1.5 h, 150 °C, 4% over 2 steps.




**Scheme 8.** Total synthesis of darienine[52] (**7**). Conditions: a) $SOCl_2$, ethyl potassium malonate, $MgCl_2$, $NEt_3$, EtOAc, 67%; b) benzyltrimethylammonium hydroxide (catalytic), crotonaldehyde, hydroxylammonium chloride, 1,4-dioxane/AcOH (1:1), rt – 100 °C, 1 h, 57%; c) LAH, THF, rt, 16 h, 67%; d) $TBHP_{non}$, 1,2-DCE, 100 °C, 18 h, 24%; e) NBS, $H_2SO_4$ conc., 50 °C, 1 h, 69%; f) $Pd_2(dba)_3$ (catalytic), KOH, $Me_4$*t*BuXPhos (catalytic), 1,4-dioxane/$H_2O$ (1:1), 18 h, 100 °C, 32%.

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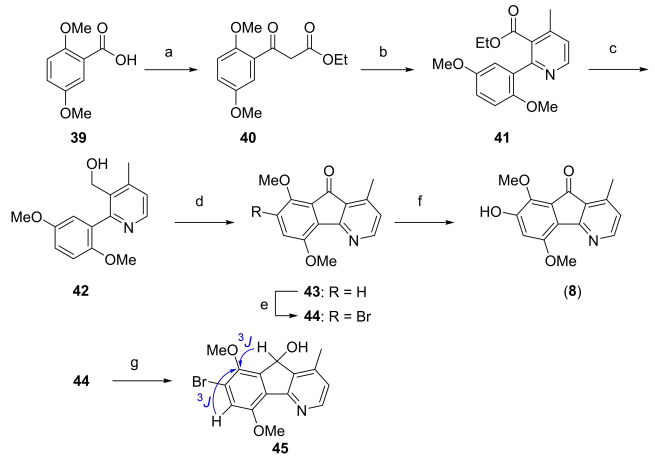
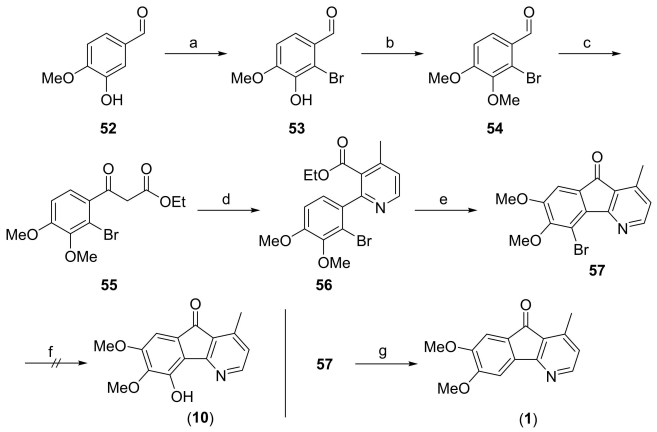


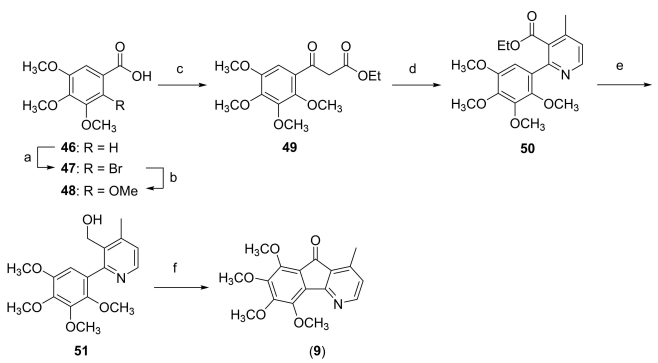
**Scheme 9.** Total synthesis of alkaloid 5,8-dimethoxy-7-hydroxyonychine[53] (**8**). Conditions: a) $SOCl_2$, ethyl potassium malonate, $MgCl_2$, $NEt_3$, EtOAc, 76%; b) benzyltrimethylammonium hydroxide (catalytic), crotonaldehyde, hydroxylammonium chloride, 1,4-dioxane/AcOH (1:1), rt – 100 °C, 1 h, 45%; c) LAH, THF, 18 h, 58%; d) $TBHP_{non}$, 1,2-DCE, 100 °C, 18 h, 21% e) NBS, $H_2SO_4$ conc. 50 °C, 1.5 h, 91%; f) $Pd_2(dba)_3$ (catalytic), KOH, $Me_4$*t*BuXPhos (catalytic), 1,4-dioxane/$H_2O$ (1:1), 18 h, 100 °C, 59%; g) $NaBH_4$, MeOH, rt, 1 h, 85%.



**Scheme 11.** Total synthesis of polyfothine (**1**). Conditions: a) NBS, DCM, rt, 18 h, 95%; b) $K_2CO_3$, MeI, DMF, rt, 18 h; 96% c) $SnCl_2$ (catalytic), ethyl diazoacetate, DCM, rt, 1 h, 38%; d) benzyltrimethylammonium hydroxide (catalytic), crotonaldehyde, hydroxylammonium chloride, 1,4-dioxane/AcOH (1:1), rt – 100 °C, 1 h, 31%; e) PPA, 140 °C, 1 h, 10%; f) $Pd_2(dba)_3$ (catalytic), KOH, $Me_4$*t*BuXPhos (catalytic), 1,4-dioxane/$H_2O$ (1:1), 18 h, 100 °C, trace amounts. g) first $Bpin_2$, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, KOAc, DMF, 80 °C, 18 h, then $NaOH_{aq}$, $H_2O_2$, 0 °C – rt, 66%.

For the synthesis of 5,6,7,8-tetramethoxyonychine[35c] (**9**), the precursor carboxylic acid **48** had to first be prepared from commercially available 3,4,5-trimethoxybenzoic acid (**46**) *via* bromination and ensuing copper(I)-catalyzed methoxylation[55] of aryl bromide **47** (Scheme 10). Pyridine **51** was prepared from here as usual. A final cyclization of pyridinemethanol **51** with TBHP afforded the natural product **9** with a yield of 14%.

Next, we attempted to synthesize both natural products polyfothine (**1**) and 5-hydroxy-6,7-dimethoxyonychine (**10**) (Scheme 11). Precursor aldehyde **54** was herein prepared from isovanillin (**52**) by way of regioselective bromination[56] and subsequent *O*-methylation.[57] Aldehyde **54** was then converted to nicotinic acid ester **56** following our established protocols. Different from other routes, the absence of an alkoxy group at C-2′ of the intermediate 2-arylnicotinic acid ester **56** allowed us to employ PPA for the ring closure reaction and circumvent the additional ester reduction step since inadvertent lactone formation was not an issue here. This, however, gave bromoazafluorenone **57** in an unexpectedly low yield of 10%. Nevertheless, with azafluorenone **57** in hand, both natural products **1** and **10** should be easily accessible *via* hydrogenolysis of the bromo substituent, for **1**, and the established bromide-to-phenol conversion we used in our previous syntheses, for **10**, respectively. Unfortunately, attempts to achieve the latter conversion were unsuccessful. During the bromide-to-phenol conversion, the majority of the starting material **57** was not consumed and only trace amounts of the desired product 5-hydroxy-6,7-dimethoxyonychine (**10**) were detected. An attempted bromide-to-phenol conversion *via* a two-step Miyaura borylation/borane oxidation[58] gave, under ring debromination, natural product polyfothine (**1**) instead with a yield of 66%.



**Scheme 10.** Synthesis of 5,6,7,8-tetramethoxyonychine[35c] (**9**). Conditions: a) NBS, MeCN, rt, 16 h, 70%; b) Na, MeOH, CuBr, 70 °C, 18 h, 97%; c) $SOCl_2$, ethyl potassium malonate, $MgCl_2$, $NEt_3$, EtOAc, 54%; d) benzyltrimethylammonium hydroxide (catalytic), crotonaldehyde, hydroxylammonium chloride, 1,4-dioxane/AcOH (1:1), rt – 100 °C, 1 h, 24%; e) LAH, THF, 18 h, 66%; f) $TBHP_{non}$, 1,2-DCE, 100 °C, 18 h, 14%.

For the synthesis of isoursuline (**3**), 2-bromo-3-hydroxybenzyldehyde (**58**) was converted into nicotinate ester **61** in the established way in three steps (Scheme 12). Cyclization with PPA afforded azafluorenone **62** with a yield of 21%. Subsequent bromide-to-phenol conversion gave isoursuline (**3**) with a yield of 46%.

Finally, in order to demonstrate that the bromide-to-phenol conversion can be generally applied in 4-azafluorenone chemistry, 7-methoxyonychine (**11**), oncodine (**12**) and 6,8-dihydroxy-7-methoxyonychine (**13**) were synthesized starting from commercially available ethyl (4-methoxybenzoyl)acetate (**63**) (Scheme 13). For construction of the pyridine ring, employment of NaH as the catalytic base gave a better yield of nicotinic acid ester **64** (23%) compared to benzyltrimethylammonium hydroxide used so far.

Subsequent PPA-catalyzed cyclization, however, afforded 7-methoxyonychine (**11**) in a low yield of 9%. Ester **64** was therefore first converted to the carboxylic acid **65** *via* alkaline

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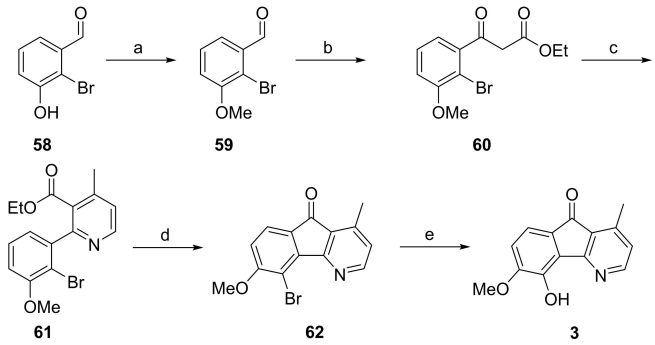
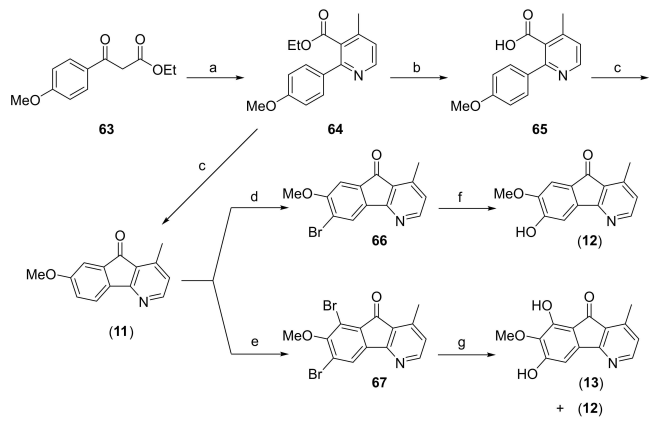



**Scheme 12.** Total synthesis of isoursuline **3**. Conditions: a) $K_2CO_3$, MeI, DMF, rt, 18 h, 98%; b) $SnCl_2$ (catalytic), ethyl diazoacetate, DCM, rt, 1 h; c) benzyltrimethylammonium hydroxide (catalytic), crotonaldehyde, hydroxylammonium chloride, 1,4-dioxane/AcOH (1:1), rt – 100 °C, 1 h, 18% over two steps; d) PPA, 140 °C, 1 h, 21%; e) $Pd_2(dba)_3$ (catalytic), KOH, $Me_4$*t*BuXPhos (catalytic), 1,4-dioxane/$H_2O$ (1:1), 18 h, 100 °C, 46%.




**Scheme 13.** Total synthesis of 7-methoxyonychine[59] (**11**), oncodine[35b] (**12**) and 6,8-dihydroxy-7-methoxyonychine[60] (**13**). Conditions: a) NaH (catalytic), crotonaldehyde, hydroxylammonium chloride, 1,4-dioxane/AcOH (1:1), rt – 100 °C, 1 h, 23%; b) KOH, $H_2O$/EtOH, 100 °C, 16 h; c) PPA, 140 °C, 1.5 h, 9% directly from **64**, 15% over two steps from **64** and **65**; d) NBS (1.1 equiv), $H_2SO_4$ conc. 50 °C, 1.5 h, 91%; e) NBS (2.1 equiv), $H_2SO_4$ conc. 50 °C, 1.5 h, 76%; f) $Pd_2(dba)_3$ (catalytic), KOH, $Me_4$*t*BuXPhos (catalytic), 1,4-dioxane/$H_2O$ (1:1), 24 h, 100 °C, 72%; g) $Pd_2(dba)_3$ (catalytic), KOH, $Me_4$*t*BuXPhos (catalytic), 1,4-dioxane/$H_2O$ (1:1), 24 h, 100 °C, 24% for (**13**) and 63% for (**12**).

ester hydrolysis before reaction thereof with PPA gave 7-methoxyonychine (**11**) in a somewhat higher yield of 15% over two steps. 7-Methoxyonychine (**11**) has been previously synthesized by Pan et al. in comparable overall yield using a similar methodology where the carboxylic acid **65** was first converted to the acyl chloride prior to $AlCl_3$-catalyzed cyclization.[24] Bromination of 7-methoxyonychine (**11**) with 1.1 and 2.1 equivalents of NBS afforded the 6-bromo derivative **66** and 6,8-dibromo derivative **67** in high yields, respectively. The 6-bromo derivative **66** was converted to oncodine (**12**) in 72% yield using our well-tried bromide-to-phenol conversion protocol. The same reaction with the 6,8-dibromo derivative **67**, however, gave a separable mixture of the desired alkaloid 6,8-dihydroxy-7-methoxyonychine (**13**) and oncodine (**12**) in yields of 24% and 63%, respectively.

Bearing in mind the respective bromide-to-phenol conversions discussed previously, no clear pattern can be established for educts bearing bromide substituents at C-5 and C-8, as they are either readily converted (for 5-bromo-6-methoxyonychine **62**), very sluggish to react (for 5-bromo-6,7-dimethoxyonychine **57**) or susceptible to reductive debromination (for 6,8-dibromo-7-methoxyonychine **67**). Conversions of the educts bearing bromide substituents at C-6 and C-7 proceeded smoothly and formation of debromination products was not observed.

## Conclusion

In conclusion, we developed a general method to synthesize a variety of 4-azafluoren-9-one alkaloids with a broad spectrum of oxygenation patterns at the phenyl ring, including C-5-oxygenated 4-azafluoren-9-ones, which are virtually inaccessible with conventional strong acid media cyclization of 2-arylnicotinates. Key steps include intramolecular radical acylation of 2-aryl-3-(hydroxymethyl)pyridines and regioselective introduction of bromo substituents as latent hydroxy groups, followed by bromide-to-phenol conversions. While the overall yields of these multi-step total syntheses are low, total syntheses of the alkaloids muniranine (**6**), darienine (**7**), 5,8-dimethoxy-7-hydroxyonychine (**8**), 5,6,7,8-tetramethoxyonychine (**9**) and 6,8-dihydroxy-7-methoxyonychine (**13**) are reported here for the first time in the literature. Furthermore, alternative total syntheses of the alkaloids polyfothine (**1**), isoursuline (**3**), onychine (**4**), ursuline (**5**), 7-methoxyonychine (**11**), oncodine (**12**), polynemoraline C (**14**) and eleven unnatural congeners were accomplished by using crucial steps of this new methodology. With this work, we close a significant gap in the methods for total synthesis of 4-azafluorenone alkaloids and demonstrated the utility of our methods by first total synthesis of five alkaloids and confirmation of the postulated structures. Our protocol opens the door for flexible synthesis of highly substituted 4-azafluorenones, and we are confident that it will be of significant value in both natural products and medicinal chemistry.

## Experimental Section

All solvents were purchased from commercial sources and used without further purification. Solvents were dried, if necessary, according to standard methods and stored over activated molecular sieves under a nitrogen atmosphere. Standard vacuum-line techniques were used, and glassware was flame- or oven-dried prior to use. Reactions were monitored *via* thin-layer chromatography (TLC) using POLYGRAM SIL G/UV254 polyester sheets coated with 0.2 mm silica gel (Macherey-Nagel). Plates were visualized using UV light (254 nm or 365 nm). Reaction monitoring was performed by mass spectrometry using an atmospheric pressure solids analysis probe (ASAP) with atmospheric pressure chemical ionization (APCI) on an expression LCMS device (Advion, Ithaca, USA). Products were purified by flash column chromatography (normal-phase silica gel chromatography) using $SiO_2$ 60 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck. Melting points were measured with a Büchi Schmelzpunktapparatur B-540 and are reported in °C. Infrared spectra were recorded from 4000 to

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650 $cm^{-1}$ on a PERKIN ELMER Spectrum BX-59343 FT-IR instrument. A Smiths Detection DuraSamp IR II Diamond ATR sensor was used for detection. The absorption bands are reported in wavenumbers ($cm^{-1}$). NMR spectra ($^1H$ NMR, $^{13}C$ NMR, DEPT, COSY, HSQC, HMBC) were recorded using Avance III HD 400 MHz Bruker BioSpin and Avance III HD 500 MHz Bruker BioSpin spectrometers ($^1H$ NMR: 400 MHz and 500 MHz, $^{13}C$ NMR: 101 MHz and 126 MHz) and the deuterated solvent stated. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Multiplicities are denoted as s (singlet), d (doublet), t (triplet), q (quartet) and derivatives thereof. Coupling constants *J* are given in Hz. High-resolution mass spectrometry (HRMS) was performed using a Jeol MStation 700 or JMS GCmate II Jeol instrument for electron impact ionization (EI). A Thermo Finnigan LTQ was used for electrospray ionization (ESI). For a comprehensive investigation on GC-MS behavior of the 4-azafluorenones prepared as part of this study, see ref. [61].

## General procedures

**General procedure 1 A: Synthesis of β-ketoesters:**[47] A Schlenk flask was charged with $SnCl_2$ (0.25 equiv.) under an $N_2$ atmosphere after which dry DCM (5 mL per mmol aldehyde) and ethyl diazoacetate (1.2 equiv.) were added. The aldehyde (1.0 equiv.), dissolved in dry DCM, was then added dropwise to this suspension and the mixture stirred at rt until gas evolution stopped. The suspension was filtered, the filter cake washed with DCM and the filtrate evaporated under reduced pressure to give the crude product.

**General procedure 1B: Synthesis of β-ketoesters**: The carboxylic acid was dissolved in DCM or toluene (5 mL per mmol). After adding $SOCl_2$ (1.5–10 equiv.) the mixture was heated to reflux. After 2 h, the volatiles were removed under reduced pressure.

To a mixture of potassium ethyl malonate (1.3–1.5 equiv.) in EtOAc (5.0 mL per mmol acid chloride) $NEt_3$ (2.2–3.5 equiv.), and subsequently $MgCl_2$ (1.7–2.5 equiv.) were added at 0 °C. The mixture was then stirred at 35 °C for 6 h. After cooling the reaction to 0 °C, the crude acyl chloride (1.0 equiv.) was added dropwise over 30 min. The mixture was stirred overnight at rt and then cooled to 0 °C before acidifying with HCl (2 M) dropwise to pH ~ 4. The aqueous layer was separated and extracted with EtOAc. The combined organic phases were washed with HCl (2 M) followed by $H_2O$ and then concentrated under reduced pressure.

**General procedure 2: Preparation of nicotinic acid esters:**[22b] Benzyltrimethylammonium hydroxide (0.22 equiv.) and crotonaldehyde (1.3–1.5 equiv.) were added consecutively to a solution of β-ketoester (1.0 equiv.) in 1,4-dioxane (0.5 mL per mmol β-ketoester) under an $N_2$ atmosphere and the resulting solution was stirred for 30 minutes. Hydroxylammonium chloride and AcOH (0.50 mL per mmol β-ketoester) were added, and the solution was heated to reflux for 30 minutes. The mixture was allowed to cool to room temperature before it was poured into water and alkalized with $K_2CO_3$ until no further gas evolution could be observed. The mixture was extracted with EtOAc and the combined organic phases were washed with water and brine. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified via flash column chromatography.

**General procedure 3: Reduction of esters to give primary alcohols:**[44] LAH (2.0 equiv.) was added to a solution of ester (1.0 equiv.) in dry THF (5 mL per mmol) and the mixture was stirred overnight. In case of incomplete conversion (TLC control), additional LAH (2.0 equiv.) was added. Once the reaction had completed, the mixture was quenched by dropwise adding MeOH and then water consecutively until no further gas evolution could be observed. The suspension was stirred an additional 30 minutes, then filtered and concentrated under reduced pressure to dryness. The residue was taken up in EtOAc and washed with water and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography.

**General procedure 4 A: Ester hydrolysis to give carboxylic acids**: KOH (4.0 equiv.) was added to a solution of the ester (1.0 equiv.) dissolved in a mixture of ethanol and water (2 : 1, 2.0 mL per mmol ester) and the resulting solution was heated to reflux overnight. After cooling to room temperature, the ethanol was removed under reduced pressure. Additional water was added to the concentrate and the solution was acidified to pH 5–6 with HCl (2 M), and the resulting precipitate was collected by filtration and washed with water. The crude product was further purified by flash column chromatography on silica gel.

**General procedure 4B: Ester hydrolysis to give carboxylic acids**: KOH (4.0 equiv.) was added to a solution of the ester (1.0 equiv.) dissolved in a mixture of ethanol and water (2 : 1, 2.0 mL per mmol ester) and the resulting solution was heated to reflux overnight. After cooling to room temperature and acidification to pH 5–6 with HCl (2 M), the solvent was removed under reduced pressure. The resulting crude product was washed on a bed of celite with EtOAc and then eluted with DCM/MeOH (4 : 1). The product was used in the next step without further purification.

**General procedure 5: Carboxylic acid reduction to give primary alcohols:**[49] Borane-dimethylsulfide (3.0 equiv.) and trimethylborate (3.0 equiv.) were added to the carboxylic acid (1.0 equiv.) in dry THF (2 mL per mmol carboxylic acid) at 0 °C under an $N_2$ atmosphere. The resulting solution was stirred at rt for 18 h, cooled to 0 °C, quenched with MeOH and evaporated under reduced pressure. After adding water to the residue, the resulting mixture was extracted with EtOAc and the combined organic phases were washed with water and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

**General procedure 6: TBHP-mediated cyclization:**[43] TBHP in nonane or decane (5.5 M) was added to a solution of the pyridinemethanol (1.0 equiv.) in 1,2-DCE (4.0 mL per mmol) in a vial lined with a teflon cap and the resulting mixture was heated to 100 °C for 18 h. The solvent was evaporated under reduced pressure and the crude product purified by flash column chromatography on silica gel.

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**General procedure 7: Bromination:**[62] NBS (1.1 equiv.) was added to a solution of the azafluorenone (1.0 equiv.) in concentrated sulfuric acid (0.50 mL per mmol azafluorenone) in a preheated oil-bath at 50 °C under vigorous stirring. After 1 h, the reaction mixture was poured carefully into water and alkalized with aqueous ammonia solution (32 %) until a precipitate formed. The suspension was extracted with EtOAc, the combined organic phases washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

**General procedure 8: Bromide-to-phenol conversion:**[50] A glass tube with an aluminum cap and septum containing a stir bar was charged with bromoazafluorenone (1.0 equiv.), $Pd_2dba_3$ (4.0 mol%), $Me_4$*t*ButylXphos (8.0 mol%) and KOH (4.0 equiv.). The tube was evacuated and backfilled with nitrogen three times, after which dry 1,4-dioxane was added (1.0 mL per mmol aryl bromide). The mixture was stirred in a preheated oil bath (100 °C) for 24 h. The reaction mixture was cooled to room temperature and acidified with dilute aqueous HCl. The resulting mixture was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

**General procedure 9: *O*-Methylation of phenols**: $K_2CO_3$ (2.0 equiv.) and MeI (1.1 equiv.) were added subsequently to a solution of the phenol in DMF (1.0 mL per mmol). The mixture was stirred at rt overnight. After the reaction had completed, the mixture was poured into diluted HCl (2 M) and extracted with EtOAc. The organic phases were washed with water and brine, dried with $MgSO_4$, and then filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

**General procedure 10: PPA-mediated cyclization**: A flame-dried flask was charged with the 2-arylnicotinate ester and PPA (10 mg per mg ester) under an $N_2$ atmosphere and the mixture was heated to 150 °C for 1.5 h under vigorous stirring. The mixture was then hydrolyzed with water under ice-cooling, and the resulting suspension extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

## Supporting Information

Additional references cited within the Supporting Information.[63]

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## *Conflict of Interests*

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** alkaloids · 4-azafluorenones · cyclization · intramolecular radical acylation · natural products · total synthesis

[1] a) D. Tadić, B. K. Cassels, M. Leboeuf, A. Cavé, *Phytochemistry* **1987**, *26*, 537–541; b) M. O. F. Goulart, A. E. G. Santana, A. B. De Oliveira, G. G. De Oliveira, J. G. S. Maia, *Phytochemistry* **1986**, *25*, 1691–1695.
[2] a) S. Prachayasittikul, P. Manam, M. Chinworrungsee, C. Isarankura-Na-Ayudhya, S. Ruchirawat, V. Prachayasittikul, *Molecules* **2009**, *14*, 4414–4424; b) J. Koyama, I. Morita, N. Kobayashi, T. Osakai, Y. Usuki, M. Taniguchi, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1079–1082; c) D. Addla, Bhima, B. Sridhar, A. Devi, S. Kantevari, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7475–7480; d) M. Abdul Talip, S. Azziz, W. Chee Fah, K. Awang, H. Naz, Y. Mhd Bakri, M. Ahmad, M. Litaudon, *Nat. Prod. Sci.* **2017**, *23*, 151–156.
[3] C. D. Hufford, S. Liu, A. M. Clark, B. O. Oguntimein, *J. Nat. Prod.* **1987**, *50*, 961–964.
[4] A. I. Waechter, A. Cavé, R. Hocquemiller, C. Bories, V. Muñoz, A. Fournet, *Phytother. Res.* **1999**, *13*, 175–177.
[5] C. Rentzea, N. Meyer, J. Kast, P. Plath, H. Koenig, A. Harreus, U. Kardorff, M. Gerber, H. Walter (BASF SE), EP 0680471 A1,**1994**.
[6] a) N. Marquise, F. Chevallier, E. Nassar, M. Frédérich, A. Ledoux, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, T. Roisnel, V. Dorcet, F. Mongin, *Tetrahedron* **2016**, *72*, 825–836; b) K. Pumsalid, H. Thaisuchat, C. Loetchutinat, N. Nuntasaen, P. Meepowpan, W. Pompimon, *Nat. Prod. Commun.* **2010**, *5*, 1931–1934; c) J. H. G. Lago, M. H. Chaves, M. C. C. Ayres, D. G. Agripino, M. C. M. Young, *Planta Med.* **2007**, *73*, 292–295.
[7] G. Heintzelman, K. Averill, J. Dodd, K. Demarest, Y. Tang, P. Jackson, (Ortho-Mcneil Pharmaceutical Inc.), WO 2003088963A1, **2003**.
[8] K. J. Stauffer, P. D. Williams, H. G. Selnick, P. G. Nantermet, C. L. Newton, C. F. Homnick, M. M. Zrada, S. D. Lewis, B. J. Lucas, J. A. Krueger, B. L. Pietrak, E. A. Lyle, R. Singh, C. Miller-Stein, R. B. White, B. Wong, A. A. Wallace, G. R. Sitko, J. J. Cook, M. A. Holahan, M. Stranieri-Michener, Y. M. Leonard, J. J. Lynch, D. R. McMasters, Y. Yan, *J. Med. Chem.* **2005**, *48*, 2282–2293.
[9] C. Safak, R. Simsek, Y. Altas, S. Boydag, K. Erol, *Boll. Chim. Farm.* **1997**, *136*, 665–669.
[10] E. M. K. Wijeratne, L. B. De Silva, T. Kikuchi, Y. Tezuka, A. A. L. Gunatilaka, D. G. I. Kingston, *J. Nat. Prod.* **1995**, *58*, 459–462.
[11] D. Mueller, R. A. Davis, S. Duffy, V. M. Avery, D. Camp, R. J. Quinn, *J. Nat. Prod.* **2009**, *72*, 1538–1540.
[12] T. Kosuge, A. Senoo, H. Ohrui, M. Muratsubaki (Canon Inc.), US8110685B2, **2012**.
[13] H. L. Wang, J. W. Wei, *Chin. J. Physiol.* **2012**, *55*, 101–107.
[14] M. Gao, H. Su, Y. Lin, X. Ling, S. Li, A. Qin, B. Z. Tang, *Chem. Sci.* **2017**, *8*, 1763–1768.
[15] M. E. L. Dealmeida, R. Braz Filho, M. V. V. Bulow, O. R. Gottlieb, J. G. S. Maia, *Phytochemistry* **1976**, *15*, 1186–1187.
[16] J. Koyama, T. Sugita, Y. Suzuta, H. Irie, *Heterocycles* **1979**, *12*, 1017–1019.
[17] B. F. Bowden, K. Picker, E. Ritchie, W. C. Taylor, *Aust. J. Chem.* **1975**, *28*, 2681–2701.
[18] a) N. S. Prostakov, A. T. Soldatenkov, P. K. Radzhan, V. O. Fedorov, A. A. Fomichev, V. A. Rezakov, *Chem. Heterocycl. Compd.* **1982**, *18*, 390–394; b) N. S. Prostakov, G. A. Vasil'ev, V. P. Zvolinskii, A. V. Varlamov, A. A. Savina, O. I. Sorokin, N. D. Lopatina, *Chem. Heterocycl. Compd.* **1975**, *11*, 971–975.
[19] A. Padwa, T. M. Heidelbaugh, J. T. Kuethe, *J. Org. Chem.* **2000**, *65*, 2368–2378.
[20] B. C. Hong, M. S. Hallur, J. H. Liao, *Synth. Commun.* **2006**, *36*, 1521–1528.

[21] M. Nitta, M. Ohnuma, Y. Lino, *J. Chem. Soc. Perkin Trans. 1* **1991**, *(5)*, 1115–1118.
[22] a) T. Alves, A. B. Deoliveira, V. Snieckus, *Tetrahedron Lett.* **1988**, *29*, 2135–2136; b) F. Bracher, *Arch. Pharm.* **1989**, *322*, 293–294; c) S. Taghavi-Moghadam, C. D. Kwong, J. A. Secrist, S. I. Khan, A. M. Clark, *Bioorg. Med. Chem.* **2016**, *24*, 6119–6130; d) S. Zhang, L. Y. Liao, F. Zhang, X. F. Duan, *J. Org. Chem.* **2013**, *78*, 2720–2725; e) H. Achenbach, A. Schwinn, *Arch. Pharm.* **1994**, *327*, 755–762; f) M. Arita, S. Yokoyama, H. Asahara, N. Nishiwaki, *Synthesis* **2019**, *51*, 2007–2013.
[23] J. Zhang, A.-R. O. el-Shabrawy, M. A. el-Shanawany, P. L. Schiff, D. J. Slatkin, *J. Nat. Prod.* **1987**, *50*, 800–806.
[24] E. Pan, S. G. Cao, P. J. Brodie, M. W. Callmander, R. Randrianaivo, S. Rakotonandrasana, E. Rakotobe, V. E. Rasamison, K. TenDyke, Y. C. Shen, E. M. Suh, D. G. I. Kingston, *J. Nat. Prod.* **2011**, *74*, 1169–1174.
[25] R. Sreekumar, P. Rugmini, R. Padmakumar, *Synth. Commun.* **1998**, *28*, 2071–2075.
[26] Y. S. Chun, J. H. Lee, J. H. Kim, Y. O. Ko, S.-G. Lee, *Org. Lett.* **2011**, *13*, 6390–6393.
[27] F. Palacios, E. Herrán, C. Alonso, G. Rubiales, B. Lecea, M. Ayerbe, F. P. Cossío, *J. Org. Chem.* **2006**, *71*, 6020–6030.
[28] a) J. K. Laha, K. P. Jethava, S. Patel, *Org. Lett.* **2015**, *17*, 5890–5893; b) J. K. Laha, K. P. Jethava, S. Patel, K. V. Patel, *J. Org. Chem.* **2017**, *82*, 76–85.
[29] K. Mishra, A. K. Pandey, J. B. Singh, R. M. Singh, *Org. Biomol. Chem.* **2016**, *14*, 6328–6336.
[30] a) G. A. Kraus, A. Kempema, *J. Nat. Prod.* **2010**, *73*, 1967–1968; b) N. Marquise, V. Dorcet, F. Chevallier, F. Mongin, *Org. Biomol. Chem.* **2014**, *12*, 8138–8141.
[31] K. N. Clary, T. G. Back, *Synlett* **2010**, *(18)*, 2802–2804.
[32] A. S. Rebstock, F. Mongin, F. Trecourt, G. Queguiner, *Tetrahedron* **2004**, *60*, 2181–2186.
[33] T. H. Tong, H. N. C. Wong, *Synth. Commun.* **1992**, *22*, 1773–1782.
[34] Y. Chikayuki, T. Miyashige, S. Yonekawa, A. Kirita, N. Matsuo, H. Teramoto, S. Sasaki, K. Higashiyama, T. Yamauchi, *Synthesis* **2020**, *52*, 1113–1121.
[35] a) C. Mérienne, G. J. Arango, D. Cortes, B. K. Cassels, A. Cavé, *Phytochemistry* **1987**, *26*, 2093–2098; b) É. Bou-Abdallah, A. Jossang, D. Tadic', M. Lebœuf, A. Cavé, *J. Nat. Prod.* **1989**, *52*, 273–278; c) B. I. Chen, Q. Ye, B. Li, G. Zhang, *Indian J. Heterocycl. Chem.* **2002**, *12*, 81–82; d) J. Koyama, T. Okatani, K. Tagahara, H. Irie, *Heterocycles* **1989**, *29*, 1649–1654; e) S. Faizi, R. A. Khan, S. Azher, S. A. Khan, S. Tauseef, A. Ahmad, *Planta Med.* **2003**, *69*, 350–355; f) X. Song, G. Chen, C. Han, T. Shao, L. Wu, X. Li (Hainan Normal University, Hainan Institute of Science & Technology), CN105037267, **2015**.
[36] D. Tadic, B. K. Cassels, A. Cave, *Heterocycles* **1988**, *27*, 407–421.
[37] F. Bracher, *Synlett* **1991**, *1991*, 95–96.
[38] Y. Tagawa, K. Yamagata, K. Sumoto, *Lett. Org. Chem.* **2006**, *3*, 759–763.
[39] J. M. Schmidt, G. B. Tremblay, M. Pagé, J. Mercure, M. Feher, R. Dunn-Dufault, M. G. Peter, P. R. Redden, *J. Med. Chem.* **2003**, *46*, 1289–1292.
[40] F. Pünner, J. Schieven, G. Hilt, *Org. Lett.* **2013**, *15*, 4888–4891.
[41] Z.-M. Lu, Q.-J. Zhang, R.-Y. Chen, D.-Q. Yu, *J. Asian Nat. Prod. Res.* **2008**, *10*, 656–664.
[42] F. Bracher, *Arch. Pharm.* **1992**, *325*, 645–648.
[43] I. A. P. Jourjine, L. Zeisel, J. Krauß, F. Bracher, *Beilstein J. Org. Chem.* **2021**, *17*, 2668–2679.
[44] D. J. Kempf, H. L. Sham, K. C. Marsh, C. A. Flentge, D. Betebenner, B. E. Green, E. McDonald, S. Vasavanonda, A. Saldivar, N. E. Wideburg, W. M. Kati, L. Ruiz, C. Zhao, L. Fino, J. Patterson, A. Molla, J. J. Plattner, D. W. Norbeck, *J. Med. Chem.* **1998**, *41*, 602–617.
[45] X.-F. Wu, J.-L. Gong, X. Qi, *Org. Biomol. Chem.* **2014**, *12*, 5807–5817.
[46] N. U. Hofsløkken, L. Skattebol, F. O. L. Johansson, S. K. Bertilsson, P. G. Andersson, J. Møller, A. E. E. Senning, X.-K. Yao, H.-G. Wang, J. P. Tuchagues, M. Ögren, *Acta Chem. Scand.* **1999**, *53*, 258–262.
[47] C. R. Holmquist, E. J. Roskamp, *J. Org. Chem.* **1989**, *54*, 3258–3260.
[48] F. Bracher, *Arch. Pharm.* **1994**, *327*, 371–375.
[49] R. Quach, D. P. Furkert, M. A. Brimble, *Tetrahedron Lett.* **2013**, *54*, 5865–5868.
[50] K. W. Anderson, T. Ikawa, R. E. Tundel, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695.
[51] R. J. Clay, T. A. Collom, G. L. Karrick, J. Wemple, *Synthesis* **1993**, *1993*, 290–292.
[52] Y.-C. Wu, C.-Y. Duh, S.-K. Wang, K.-S. Chen, T.-H. Yang, *J. Nat. Prod.* **1990**, *53*, 1327–1331.
[53] N. Yoshida, J. Maximo, R. Rodrigues, R. Correia, W. Garcez, *J. Braz. Chem. Soc.* **2013**, *24*, 529–533.
[54] C. Alonso, M. Fuertes, M. González, G. Rubiales, C. Tesauro, B. R. Knudsen, F. Palacios, *Eur. J. Med. Chem.* **2016**, *115*, 179–190.
[55] H. L. Aalten, G. van Koten, D. M. Grove, T. Kuilman, O. G. Piekstra, L. A. Hulshof, R. A. Sheldon, *Tetrahedron* **1989**, *45*, 5565–5578.
[56] T. Denoël, A. Zervosen, C. Lemaire, B. Joris, M. Hervé, D. Blanot, G. Zaragoza, A. Luxen, *Org. Biomol. Chem.* **2014**, *12*, 9853–9863.
[57] D. P. Venter, J. H. Langenhoven, *S. Afr. J. Chem.* **1996**, *49*, 40.
[58] J.-H. Lee, C.-G. Cho, *Org. Lett.* **2016**, *18*, 5126–5129.
[59] S. Prachayasittikul, P. Manam, M. Chinworrungsee, C. Isarankura-Na-Ayudhya, S. Ruchirawat, V. Prachayasittikul, *Molecules* **2009**, *14*, 4414–4424.
[60] K. Pumsalid, H. Thaisuchat, C. Loetchutinat, N. Nuntasaen, P. Meepowpan, W. Pompimon, *Nat. Prod. Commun.* **2010**, *5*, 1931–1934.
[61] I. A. P. Jourjine, C. Bauernschmidt, C. Müller, F. Bracher, *Molecules* **2022**, *27*, 8217.
[62] J. Młochowski, Z. Szulc, *J. Prakt. Chem.* **1980**, *322*, 971–980.
[63] J. Koyama, T. Ogura, K. Tagahara, M. Miyashita, H. Irie, *Chem. Pharm. Bull.* **1993**, *41*, 1297–1298.
[64] P. Kathirvel, R. Anitha, S. Vasanthamani, J. Karthika, V. Tamilselvi, *Asian J. Chem.* **2017**, *29*, 2467–2469.
[65] D.-J. Barrios Antúnez, M. D. Greenhalgh, C. Fallan, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2016**, *14*, 7268–7274.
[66] K. J. Duffy, A. N. Shaw, E. Delorme, S. B. Dillon, C. Erickson-Miller, L. Giampa, Y. Huang, R. M. Keenan, P. Lamb, N. Liu, S. G. Miller, A. T. Price, J. Rosen, H. Smith, K. J. Wiggall, L. Zhang, J. I. Luengo, *J. Med. Chem.* **2002**, *45*, 3573–3575.
[67] Y. Zhu, X. Zou, F. Hu, C. Yao, B. Liu, H. Yang, *J. Agric. Food Chem.* **2005**, *53*, 9566–9570.
[68] O. Píša, S. Rádl, *Eur. J. Org. Chem.* **2016**, *2016*, 2336–2350.
[69] A. I. Meyers, J. R. Flisak, R. A. Aitken, *J. Am. Chem. Soc.* **1987**, *109*, 5446–5452.
[70] T. Aechtner, D. A. Barry, E. David, C. Ghellamallah, D. F. Harvey, A. de la Houpliere, M. Knopp, M. J. Malaska, D. Pérez, K. A. Schärer, B. A. Siesel, K. P. C. Vollhardt, R. Zitterbart, *Synthesis* **2018**, *50*, 1053–1089.
[71] N. T. T. Chau, T. H. Nguyen, A.-S. Castanet, K. P. P. Nguyen, J. Mortier, *Tetrahedron* **2008**, *64*, 10552–10557.

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