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Total synthesis of fluorenones, 4-azafluorenones and related natural products

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Erklärung

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Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

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Publications

Ilya A. P. Jourjine, Lukas Zeisel, Jürgen Krauß, Franz Bracher: Synthesis of highly substituted fluorenones *via* metal-free TBHP-promoted oxidative cyclization of 2-(aminomethyl)biphenyls. Application to the total synthesis of nobilone, *Beilstein J. Org. Chem.* **2021,** *17,* 2668–2679.

Ilya A. P. Jourjine, Carolin Bauernschmidt, Christoph Müller, Franz Bracher: A GC-MS Protocol for the Identification of Polycyclic Aromatic Alkaloids from Annonaceae, Molecules **2022**, 27, 8217.

Ilya A. P. Jourjine, Franz Bracher: Collective Total Synthesis of 4-Azafluorenone Alkaloids, European Journal of Organic Chemistry, **2023**, e202300399.

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1 Introduction

1.1 Fluorenones

1.1.1 Biological activity

9*H*-Fluoren-9-one (**1**) is a fused tricyclic ketone with a bright yellow color. Natural products containing the fluorenone skeleton and synthetic derivatives thereof exhibit a diverse range of biological activities and (nonlinear) optoelectronic properties that make them not only attractive scaffolds for drug development, but also the subject of continued research in materials science as part of e.g. polymers, organic diodes, biomarkers, transistors, or semiconductors.[1]

Dengibsin (**2**) and dengibsinin (**3**) were the first natural fluorenone derivatives to be isolated by Talapatra et al. in 1984 from *Dendrobium gibsonii*, an epiphytic plant belonging to the family of Orchidaceae and native to higher altitude mountainous regions in Asia (Figure 1).[2] Stems of the *Dendobium* species are dried and used as a tonic herb and antipyretic in traditional Chinese medicine.[3] The initially erroneous structures reported for both natural products were reassigned after total syntheses developed by Sargent[4] and later recognized to be the result of faulty interpretation of their spectral data by Talapatra and coworkers after reexamination thereof.[5] Both compounds were later also isolated from various other members of the *Dendrobium* species including *Dendrobium densiflorum*[6], *Dendrobium chrysotoxum*[7] as well as *Dendrobium farmeri*[8], but also plants like *Arundina gramnifolia*.[9] Only few biological studies on these two compounds have been conducted in which they displayed little to no activity.[10] For example, dengibsinin (**3**) showed no α-glucosidase inhibitory activities when fluorene derivatives isolated from *Dendrobium gibsonii* were tested.[11] However, dengibsin (**2**) was reported as an intermediate for patents detailing the development of alkyloxamino-substituted fluorenones as protein kinase C inhibitors[12] and precursors for drug candidates against diabetes.[13]

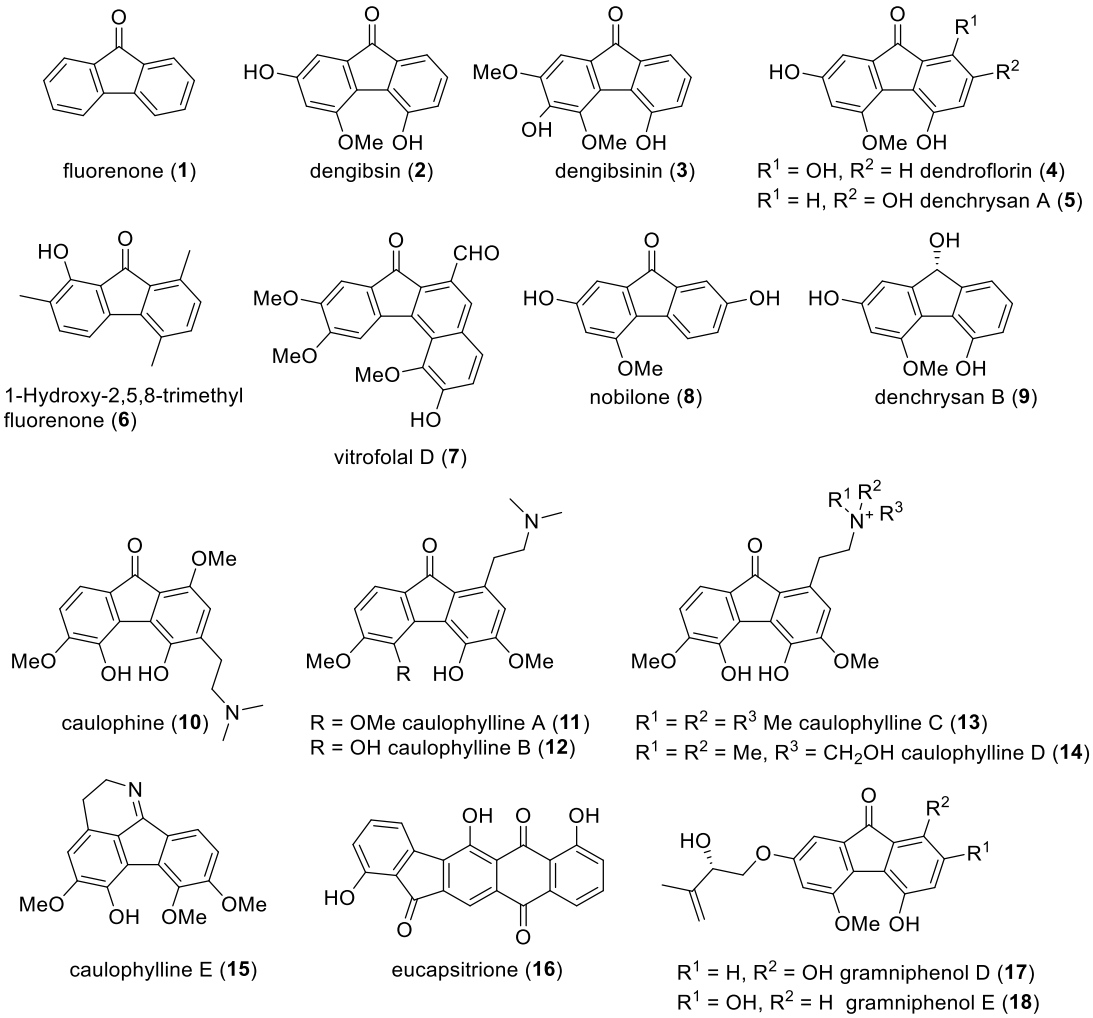


Figure 1: Representative overview of fluorenone (**1**) and related natural products. *Note*: The structure of eucapsitrione (**16**) has been called into question.[14]

Talapatra et al. also isolated dendroflorin (**4**) from *Dendrobium densiflorum* in 1984.[15] The structure originally postulated for dendroflorin (**4**) was later revised by Fan et al. in 2001.[10] The compound was also found in other members of the *Dendrobium* genus such as *Dendrobium chrysotoxum*[16], *Dendrobium brymerianum*[17] and *Dendrobium palpebrae*.[18] Dendroflorin (**4**) was shown to have an inhibitory effect on H460 human lung cancer cell line migration[17] and selective cytotoxicity against the BEL-7402 human hepatoma cell line.[16] Reportedly, it also exhibits anti-senescence activity in the MRC-5 diploid human cell line, promoting cells from the G1 phase into the S phase, and preventing the accumulation of reactive oxygen species (ROS) as determined *via* DCFH-DA (Dichlorodihydrofluorescein diacetate) assay.[19] The strong antioxidant activity of dendroflorin (**4**) was corroborated in additional studies examining the hydroxyl radical scavenging effects of isolates from *Dendrobium palpebre* in the RAW 264.7 macrophage mouse cell line *via* deoxyribose assay[18], as well as in DPPH (2,2-diphenyl-1-picrylhydrazyl) and ORAC (oxygen radical absorbance capacity) assays, where it exceeded the effects of the positive control vitamin C.[20] Dendroflorin (**4**) reportedly also inhibits nitrogen oxide production specifically in the LPS-

activated RAW 264.7 cell line[20], which has been implicated in many pathological conditions, with an IC_{50} value of 17.7 ± 3.1 μM comparable to that of the positive control L-NMMA (17.9 ± 3.2 μM).[21]

Denchrysan A (**5**) and denchrysan B (**9**) were first isolated from *Dendrobium chrysanthum* (Figure 1).[22] The former has been shown to exhibit selective cytotoxicity against the human hepatoma cell line BEL-7402 with an IC_{50}-value of 1.4 μg/mL while inactive or only weakly active against other human cancer cell lines.[16] The absolute configuration of denchrysan B (**9**) was later determined by Yang et al. as the (9*R*)-configuration *via* chiral derivatization as diastereomeric Mosher esters.[23]

1-Hydroxy-2,5,8-trimethylfluorenone (**6**) was isolated from *Tripterygium wilfordii*, a vine also colloquially referred to as “thunder god vine”, by Wu and corworkers[24], and is widespread in Asia. Its extracts are used in Chinese folk medicine, although it is not the main bioactive constituent.[25] Biological studies covering the natural product have not been published.

Vitrofolal D (**7**), a benzo[*c*]fluorenone bearing a formyl substituent first isolated from *Vitex rotundifolia* by Kawazoe et al., exhibits selective antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) with a minimum inhibitory concentration (MIC) of 32 μg/mL or less for eight out of 18 strains screened.[26]

Nobilone (**8**) was first isolated by Zhang and coworkers from *Dendrobium nobile*[20] and later from other *Dendrobium* plants such as *Dendrobium hainanense*[27], *Dendrobium palebrae*[18], and *Denrobium gibsonii*.[11] It displays higher antioxidant activity than vitamin C as determined *via* ORAC assay.[20]

Wang and coworkers isolated caulophine (**10**), bearing a *N*,*N*-dimethyl ethylamine moiety, from *Caulophyllum robustum* Maxim.[28] The compound was shown to exhibit anti-myocardial ischemia activity when screened in rat cardiac muscle cells. A preparative HPLC method for the isolation and purification of caulophine (**10**) has been developed by Wen et al., which assisted in investigation of its metabolism and execration in rats.[29] More than 50% of the treatment dose was excreted and the glucuronide conjugate and *N*-oxide of caulophine (**10**) were detected in rat urine and feces *via* LC-MS. The structurally related caulophyllines A-D (**11**-**14**) were later isolated from the same plant.[30]

Caulophylline E (**15**), a dihydroazafluoranthene also found in *Caulophyllum robustum* Maxim, has been proposed as a biosynthetic precursor for different substituted fluorenones bearing the *N*,*N*-dialkyl ethylamine motive.[28]

Eucapsitrione (**16**), featuring both a fluorenone and anthraquinone moiety, was isolated from a cyanobacterium of the genus *Eucapsis* by the Orjala group, and displayed potent and

selective activity against *M. tuberculosis* with MIC-values of 3.1 μM and 6.4 μM in relevant tuberculosis assays (MABA and LORA assays, respectively) with only limited cytotoxic properties (IC_{50} > 28 μM).[31] However, the proposed structure has been called into question *via* total synthesis and comparison of the physical properties and spectral data by Pullella et al.[14] The lack of a characteristic absorption band in the IR-spectrum suggests that the compound might not even be a fluorenone at all. A structural reassignment was deemed unfeasible based on the published spectra of the isolated natural product.

Gramniphenols D (**17**) and E (**18**) were isolated from *Arundina gramnifolia*, another plant used in traditional Chinese medicine for the treatment of inflammation and arthritis in local populations.[32] Both compounds were tested for anti-HIV-1 activity against the C8166 cell line. While not as potent as the antiretroviral drug azidothymidine used as a positive control (EC_{50} = 0.03 μg/mL), both compounds exhibited appreciable anti-HIV-1 activity with respective EC_{50}-values of 1.5 μg/mL and 1.6 μg/mL with therapeutic indices exceeding 100, respectively.

Various alkylated and benzoannelated fluorenones have also been identified as the main constituents of low polar heterocompound rock bitumen extracts from the Posidonia oil shale in northwest Germany.[33]

Given the potential of natural products bearing fluorenone pharmacophores, research on synthetic fluorenone derivatives for pharmaceutical applications has enjoyed great attention over the years.

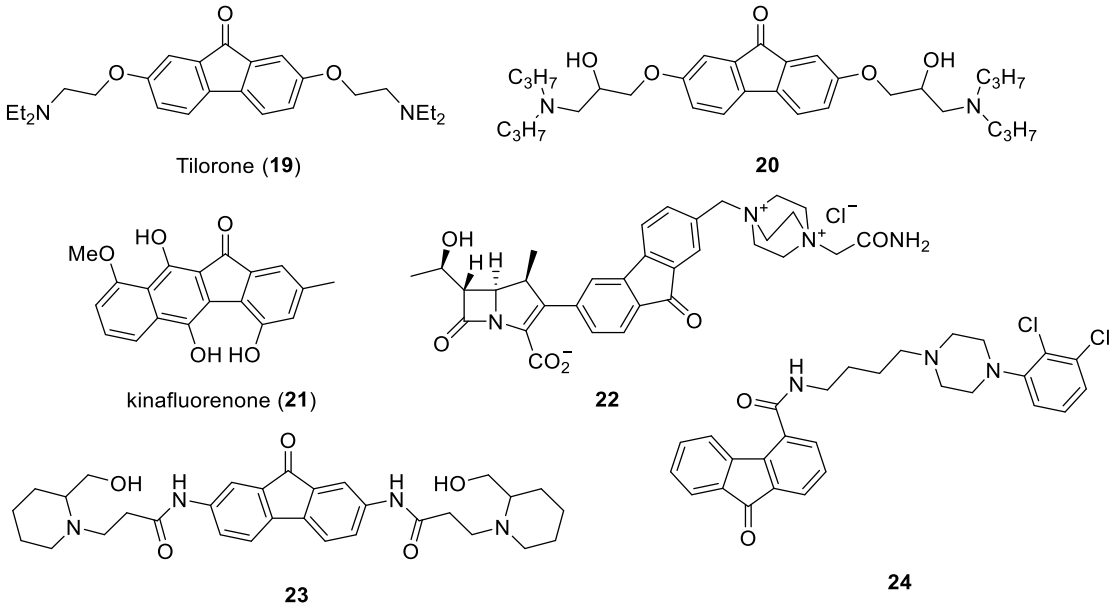


Figure 2: Selection of biologically active synthetic compounds with fluorenone scaffold.

Among the most noteworthy examples is tilorone (**19**, Figure 2), a fluorenone derivative bearing two 2-diethylaminoethoxy residues, which represents one of the first orally bioavailable small-

molecule drugs with broad antiviral activities. Developed in 1970, the antiviral activity of tilorone (**19**) was initially thought to hinge on its ability to stimulate innate immunity signaling pathways through DNA strand intercalation and the resulting induction of type I inteferons (IFN) that eventually lead to the inhibition of viral replication.[34] While increased INF production has been confirmed in mice cells upon administration of tilorone (**19**), in humans, tilorone (**19**) reportedly not only failed to induce production of inteferons to a detectable level but was also noted to be toxic[35], which may suggest different modes of action in different species. Recent studies indicate that it might bind directly to viral glycoproteins.[36] Furthermore, it causes lysosomal storage of sulphated glycosaminoglycans (GAGs) otherwise targeted for degradation *via* ionic interaction, which may have serious health implications reminiscent of mucopolysaccharidoses.[37] Meanwhile, other studies claim to show that the drug does indeed safely and effectively stimulate the human immune system by inducing the production of IFN.[38] It may be due to the partly conflicting information surrounding the drug's safety and efficacy, that it has only been approved for clinical use in a limited number of countries like Russia and other Eastern European countries for the treatment of various viral infections like influenza or acute respiratory viral infections under the trade names Amixin® and Lavomax®.[39] In recent years, interest in tilorone (**19**) and analogues thereof has seen a resurgence as they might have potential applications against several viruses such as the Ebola virus[40], herpes simplex virus[41], Mengo virus[42], West Nile Virus[43], Venezuelan equine encephalitis virus[44], and human corona viruses like MERS-CoV[45] and SARS-CoV-2[36a]. Tilorone (**19**) was also shown to be a selective agonist of the α7 nicotinic acetylcholine receptor[46], a drug target for cognitive enhancement of schizophrenia and Alzheimer's disease and a potential anti-cancer agent.[47] A very recent study shows the compound also increases the glucose uptake *in vivo* and in skeletal muscle cells by enhancing transcription of bone morphogenetic proteins, which could see potential application for the treatment of insulin resistance.[48] Naturally, efforts were made to develop tilorone (**19**) analogues with improved efficacy. One such example, fluorenone **20**, exhibits stronger anticancer activity than tilorone.[49]

Further examples of noteworthy synthetic fluorenones include kinafluorenone (**21**), a benzo[*b*]fluorenone derivative isolated from the MC1 mutant strain of *Streptomyces murayamaensis*. In the MC1 strain kinamycin production is blocked. Isolation and identification of kinafluorenone (**21**) helped establish an understanding of its biogenesis and relationship to kinamycin biosynthesis.[35] The compound itself, however, does not seem to exhibit antibiotic activity like kinamycins do.

Greenlee et al. prepared 2-fluorenonylcarbapenems bearing dicationic DABCO moieties which confer excellent water solubility to potential anti-MRSA agents.[50] 2-Arylcarbapenems bind to PBP2a, a penicillin-binding protein that mediates methicillin resistance in staphylococci.

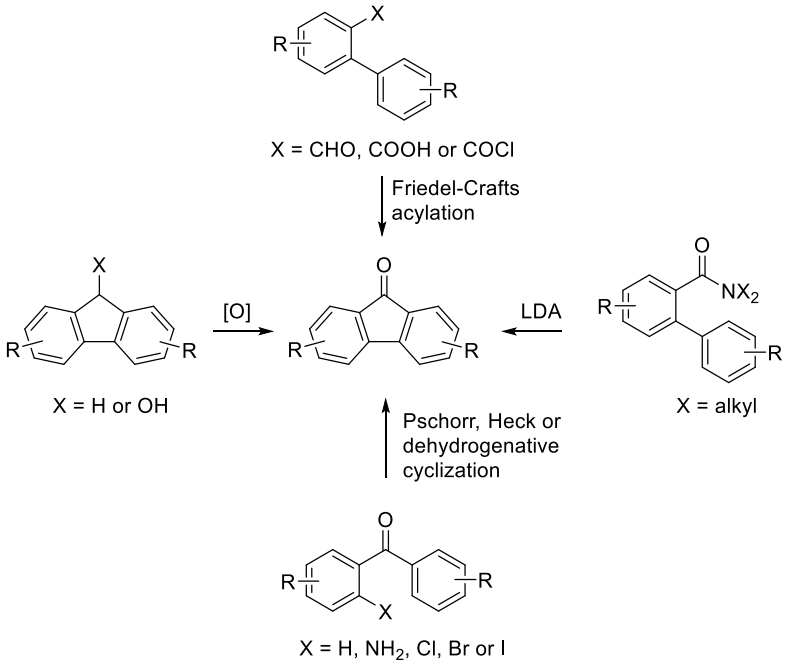
Compound **22** showed potent activity against MRSA with a MIC_{50} value of 4 μM comparable to vancomycin, an antibiotic commonly prescribed against MRSA. Introduction of a 1-β-methyl substituent at the carbapenem motif, based on structure-activity relationship studies, increased pharmacokinetic parameters to levels superior to those of imipenem, a β-lactam antibiotic.

Perry et al. developed series of 2,7-disubstituted amidofluorenones with human telomerease inhibiting properties. The most potent compound, fluorenone **23**, boasted a $^{tel}IC_{50}$ value of 8.0 μM.[51]

Fluorenone derivatives have also been demonstrated to be potentially effective neurochemical modulators. Compound **24** exhibited high dopamine D_3 receptor binding affinity and selectivity with a K_i value of 1.4 nM for D_3 and a binding ratio of 64 for D2/D3 and 1319 for D4/D3.[52]

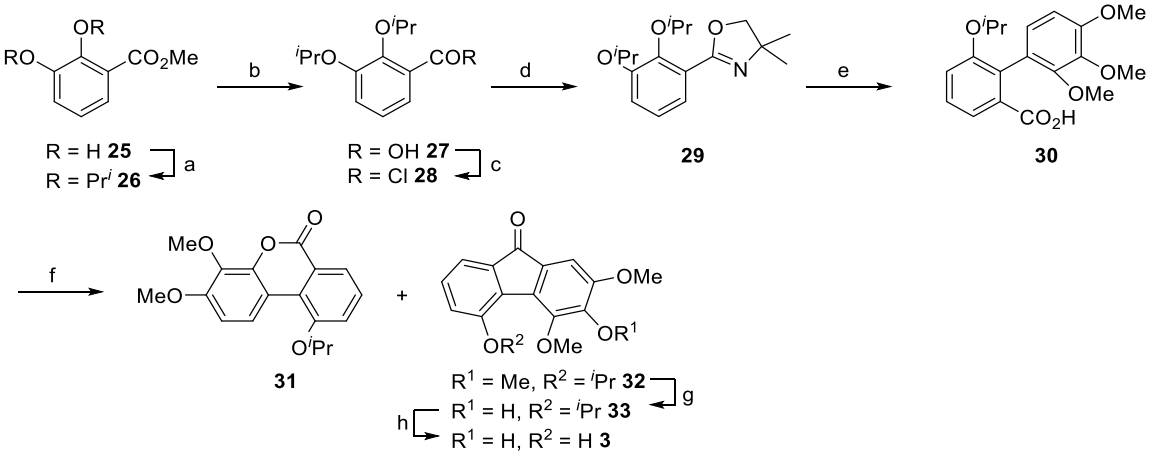
1.1.2 Synthesis of fluorenones and fluorenone-type natural products

The syntheses of fluorenones are well documented and reach back as far as the 1930s.[53] The most pervasive synthetic routes to fluorenones include intramolecular Friedel-Crafts-type acylation of biphenyl acyl chlorides[54], carboxylic acids[55], aldehydes[56], *N*-alkyl benzamides[57] and other functional groups, oxidation of fluorenols[58] or fluorenes[59], Pschorr cyclization of 2-amino diaryl ketones[60], Heck cyclization of 2-bromo diaryl ketones[61], directed remote lithiation of *N*,*N*-dialkylbiphenyl 2-carboxamides[62] and Diels-Alder reactions.[63] Many modern methods center around transition-metal-catalyzed approaches with particular attention given to intramolecular C-C bond formation *via* C-H functionalization.[64] The concept has been adopted for the development of convenient one-pot, multistep synthesis protocols.[65]



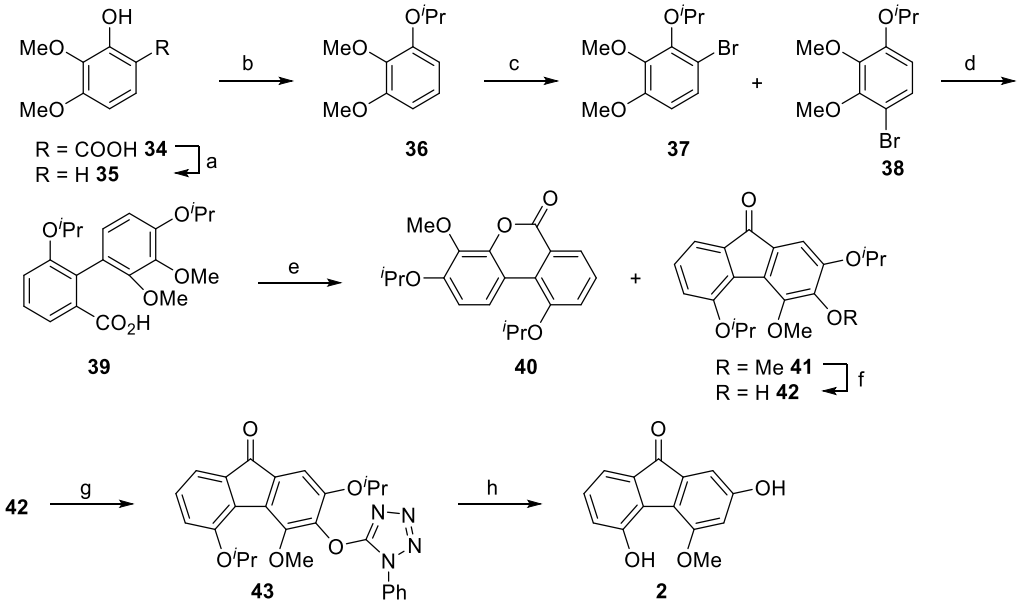
Scheme 1: Representative approaches to fluorenone synthesis.

Only a few of the fluorenone-type natural products isolated from nature have also been prepared *via* total synthesis so far. The first total syntheses were developed for dengibsin (**2**) and dengibsinin (**3**) by Sargent in 1987 (Schemes 2 and 3).[4] For both total syntheses, an appropriately substituted oxazoline building block **29** was prepared starting from ester **25**. Following the introduction of isopropyl ether protecting groups and alkaline hydrolysis, the crude carboxylic acid **27** was converted to the acyl chloride **28**. Reaction with 2-amino-2-methylpropan-1-ol gave the crude amide and further treatment with thionyl chloride the desired oxazoline **29**. From here, the oxazoline **29** was reacted with appropriately substituted bromobenzene-derived Grignard reagents to give the respective biphenyls *via ortho*-displacement of alkoxy groups in a nucleophilic aromatic substitution.[66] In the case of dengibsinin (**3**), the required bromobenzene precursor was readily available, in the case of dengibsin (**2**), the precursor **38** had to be prepared in a three-step synthesis starting from 2-hydroxy-3,4-dimethoxybenzoic acid **34**.



Scheme 2: First total synthesis of dengibsinin (**3**) by Sargent.[4] Conditions: a) 2-bromopropane, K_2CO_3, DMF, 80 °C, 18 h, 94%; b) KOH, H_2O/MeOH; c) $SOCl_2$, rt, 22 h; d) first 2-amino-2-methylpropan-1-ol, DCM, 0 °C → rt, 1.5 h; then $SOCl_2$, 0 °C → rt, 75 min, 90% over three steps; e) first Grignard reagent derived from 1-bromo-2,3,4-trimethoxybenzene, THF, rt, 3 h; then $MeNO_2$, MeI, 60 °C, 22 h; then NaOH, KOH, H_2O/MeOH; f) TFAA, DCM, rt, 6.5 h, 24% (fluorenone **32**) and 49% (lacton **31**) over two steps; g) piperidine/H_2O, reflux, 12 h, 95%; h) BCl_3, DCM, -10 °C, 15 min, 82%.

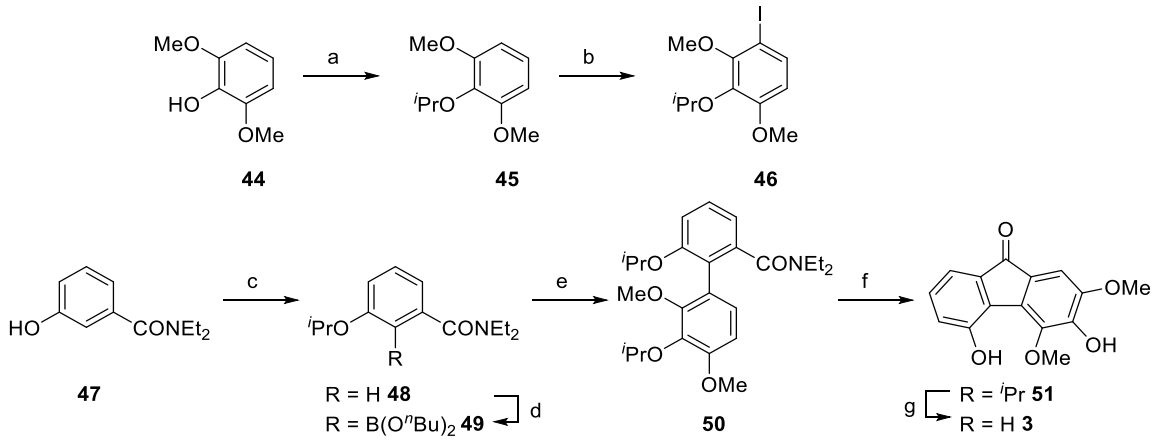
Preparation of the biphenyl carboxylic acids **30** and **39** was accomplished *via* quaternization of the oxazoline nitrogen with iodomethane and subsequent alkaline hydrolysis. The biphenyl carboxylic acids were then cyclized with trifluoroacetic anhydride (TFAA). While some amount of the desired products (24% for **32**, 15% for **41**) was furnished in both cases, unexpectedly, the major products were the corresponding lactones (49% for **31**, 38% for **40**). Dengibsinin (**3**) was furnished after regioselective *O*-demethylation of the 3-OMe group of fluorenone **32** with piperidine and subsequent removal of the isopropyl protecting group. Dengibsinin (**3**) was prepared in ten steps with an overall yield of 1.3%.



Scheme 3: First total synthesis of dengibsin (**2**) by Sargent.[4] Conditions: a) Cu_2O, 2,2'-bipyridyl, *N*,*N*-dimethylaniline, reflux, 1 h, 89%; b) 2-bromopropane, K_2CO_3, DMF, 87%; c) Br_2, AcOH, NaOAc, 30% (**37**) and 31% (**38**); d) first Grignard reagent from **38**, THF, rt, 3 h, then $MeNO_2$, MeI, 60 °C, 22 h; then NaOH, KOH, H_2O/MeOH, e) TFAA, DCM, rt, 6.5 h, 15% (fluorenone **41**) and 38% (lacton **40**) over two steps; f) piperidine/H_2O, reflux, 40 h, 81%; g) 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3, DMF, 90 °C, 22 h, 87%; h) first Pd/C (10%), benzene, ethanol/H_2O, hydrazine hydrate (98%), 6 h, then BCl_3, DCM, 0 °C ⟶ rt, 15 min, 79% over two steps.

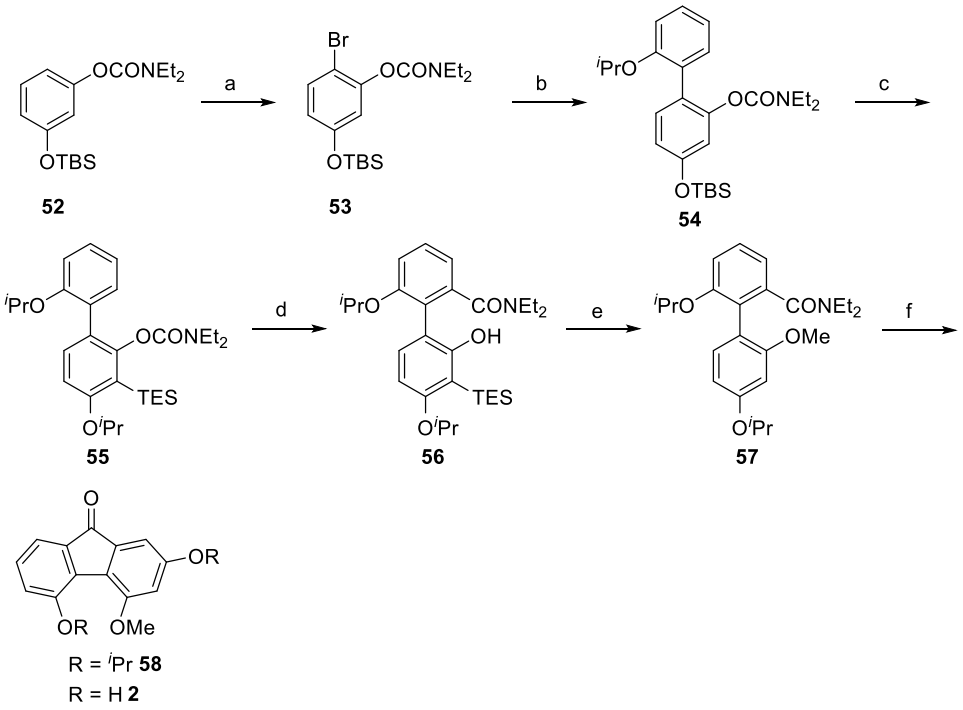
For dengibsin (**2**), the 3-hydroxyfluorenone **42** was first converted to tetrazolyl ether **43**. Dengibsin (**2**) was furnished following hydrogenolysis and subsequent deisopropylation.

A second total synthesis for dengibsinin (**3**) was developed by the Snieckus group (Scheme 4).[62] Herein, an isopropoxylated and *ortho*-borylated *N*,*N*-diethylbenzamide **49** is coupled with iodobenzene **46** under Suzuki conditions. Remote metalation of the biaryl 2-carboxamide **50** with LDA generates the 6'-lithio species which subsequently cyclizes in an intramolecular amide-RLi condensation to give fluorenone **51** and finally the natural product (**3**) after deprotection. This method of cyclization furnishes single fluorenones if one site for remote cyclization is blocked by, for example, alkoxy substituents, which also circumvents the issue of lactonization observed for Friedel-Crafts-type cyclizations. The overall yield achieved for dengibsin (**3**) was 27% in eight steps.



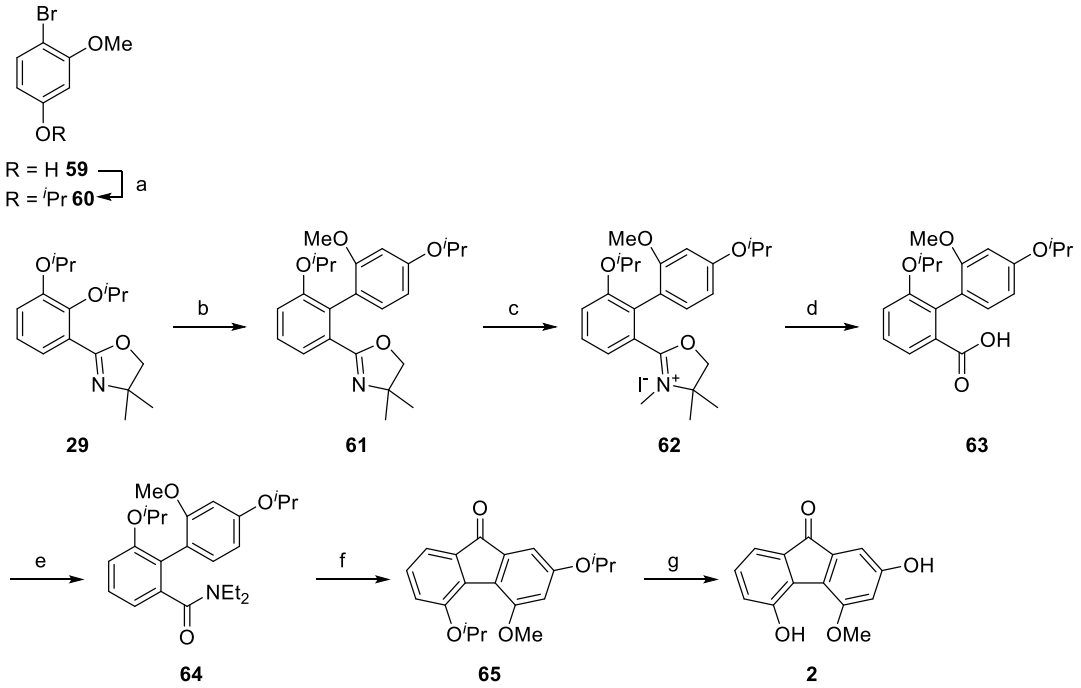
Scheme 4: Total synthesis of dengibsinin (**3**) by the Snieckus group.[62] Conditions: a) not specified; b) AgTFA, I_2, $CHCl_3$, rt, 3 h, 96%; c) K_2CO_3, KI, 2-bromopropane, MeCN, 80 °C, 48 h; 78%; d) first *s*-BuLi/TMEDA, THF, -78 °C, then $B(O^nBu)_3$, then aq NH_4Cl, 94%; e) **46**, $Pd(dppf)Cl_2$, K_3PO_4, DMF, rt, 50%; f) LDA, THF, 0 °C ⟶ rt, 67%; g) BCl_3, DCM, 0 °C, 87%.

Application of this method for an analogous synthesis of dengibsin (**2**), however, failed[67] and a different approach to metalation had to be taken (Scheme 5).[68] Herein, biaryl **54**, prepared from 3-silyloxy carbamate **52** *via* metalation-bromination and subsequent Suzuki coupling, was desilylated and isopropylated. Next, an anionic Fries rearrangment was envisaged, for which biaryl **55** was prepared by low-temperature *ortho*-metalation silylation. With the first metalation site blocked by a triethylsilyl residue, treatment with 3.0 equivalents of LDA generated the 6'-lithiated species and facilitated carbamoyl migration to give biarly **56**. Following TES-desilylation and *O*-methylation, remote metalation-cyclization and subsequent deisopropylation gave the natural product dengibsin (**2**) in eight steps and an overall yield of 13%.



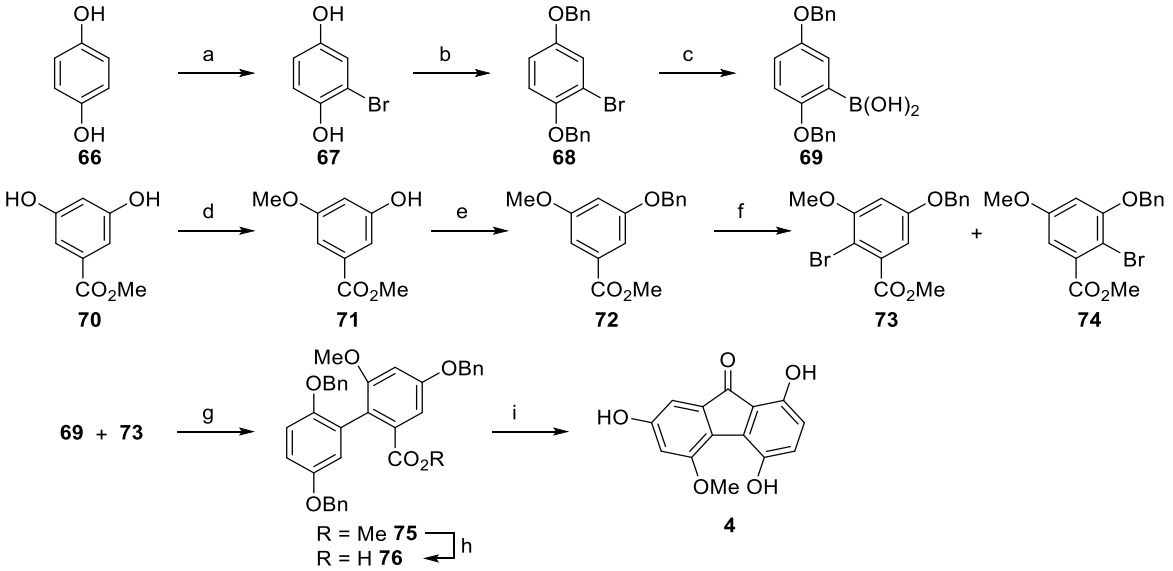
Scheme 5: Total synthesis of dengibsin (**2**) by the Snieckus group.[62] Conditions: a) first *s*-BuLi, TMEDA, THF, -100 °C; then BrF_2CCF_2Br, 82%; b) 2-isopropoxyphenyl boronic acid, $Pd(PPh_3)_4$, aqueous Na_2CO_3, DME, reflux, 68%; c) first TBAF, THF, rt; then *i*-PrI, K_2CO_3 then *s*-BuLi, TMEDA, THF, -100 °C; then TESCl, 76%; d) LDA (3.0 equiv.), THF, reflux, 61%; e) first MeI, K_2CO_3, then TFA, reflux, 87%; f) first LDA (2.5 equiv.), THF, 0 °C ⟶ rt, then BCl_3, DCM, 0 °C ⟶ rt, 56%.

Jones and Ciske published another total synthesis for dengibsin (**2**), which essentially combined the concepts of Sargent's and Snieckus' approaches to develop the to-date most efficient synthesis route for the natural product (Scheme 6).[69] The biaryl carboxylic acid **63** was constructed analogous to Sargent's method *via* oxazoline-directed nucleophilic aromatic substitution and subsequent *N*-methylation-hydrolysis. Treatment with benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphat (PyBOP), diethylamine and diisopropylethylamine (DIEA) gave the amide **64**, which was converted to dengibsin (**2**) following remote-metalation cyclization with LDA and a final deprotection step. The natural product was furnished in an overall yield of 26% in six steps.



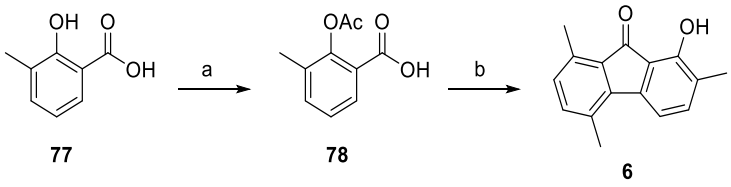
Scheme 6: Total synthesis of dengibsin (**2**) by Jones and Ciske.[69] Conditions: a) K_2CO_3, ^{i}PrI, 2-butanone, 87%; b) Mg, **60**, THF, 50 °C, 81%; c) MeI, DMSO, rt, 20 h, 94%; d) first 20 % aqueous NaOH, MeOH, reflux, then 12 M HCl_{aq}, 84%; e) PyBOP, DCM, Et_2NH, DIEA, 85%; f) LDA (4.1 equiv.), THF, -50 °C → rt, 48 h, 62%; g) BCl_3, DCM, 0 °C → rt, 76%.

The first total synthesis of dendroflorin (**4**) was accomplished in 2017 by Deng and coworkers in ten steps with an overall yield of 5.5% (Scheme 7).[70] Appropriately benzyloxylated phenylboronic acid **69** and 2-bromobenzoic acid **73** were prepared stepwise from hydroquinone (**66**) and 3,5-dihydroxybenzoic acid (**70**) *via* conventional phenol protection, bromination and *O*-methylation protocols. Coupling of both building blocks under Suzuki conditions and subsequent alkaline ester hydrolysis furnished the biphenyl carboxylic acid **76**. Simultaneous intramolecular Friedel-Crafts-type acylation and debenzylation with $AlCl_3$ at 0 °C furnished dendroflorine (**4**) in one step. Interestingly, contrary to other Friedel-Crafts-type cyclizations conducted at high temperatures, lactonization was not reported.



Scheme 7: First total synthesis of dendroflorin (**4**) by Deng et al.[70] Conditions: a) Br_2, DCM, 0 ⟶ 25 °C., 4 h, 92%; b) BnBr, K_2CO_3, acetone, reflux, 17 h, 89%; c) first *n*-BuLi, $B(OEt)_3$, THF, -78 °C ⟶ 25 °C., 12 h, then HCl_{aq} to pH = 3, 25 °C, overnight, 81%; d) Me_2SO_4, K_2CO_3, acetone, reflux, 8 h, 53%; e) BnBr, K_2CO_3, acetone, reflux, 17 h, 92%; f) NBS, MeCN, 0 °C ⟶ 25 °C; g) $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, sealed tube, 135 °C, 24 h, 84%; h) NaOH, H_2O/THF 1:1, 90 °C, 18 h; i) first oxalyl chloride, DMF, DCM, 25 °C, 3 h; then $AlCl_3$, DCM, 0 °C ⟶ 25 °C, 4.5 h, 65%.

The first total synthesis of 1-hydroxy-2,5,8-trimethylfluorenone (**6**) was reported only recently in 2021 by Liu and coworkers in a patent filed for the Jiangxi University of Traditional Chinese Medicine.[71] The total synthesis was accomplished by Pd-catalysed one-pot reaction of acetyl protected 3-methylsalicylic acid **78** with *p*-xylene, sodium persulfate, *N*-acetyl-L-isoleucine, TfOH and DMSO to give the natural product (**6**) in 43% yield. Acetylation of the starting material was necessary as the reaction did not work with the unprotected compound. The natural product was thus furnished in only two steps in a total yield of 37%.



Scheme 8: First total synthesis of 1-hydroxy-2,5,8-trimethylfluorenone (**6**) by Liu et al.[71] Conditions: a) acetyl chloride, NEt_3, DMAP, DCM, rt ⟶ reflux, 1.5 h, 85%; b) *p*-xylene, $Pd(OAc)_2$, $Na_2S_2O_8$, Ac-Ile-OH, DMSO, TfOH, 65 °C, 12 h, 43%.

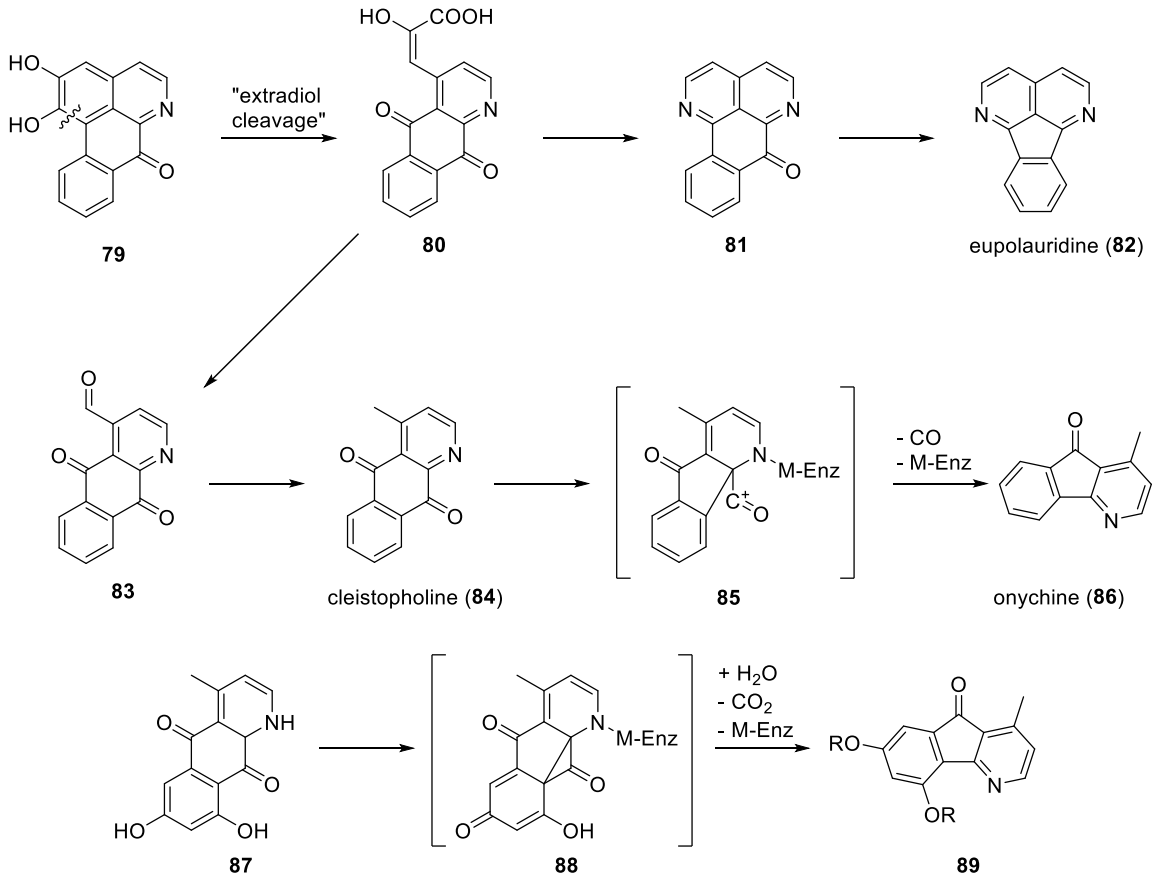
Although not cited in the patent, the method closely resembles a publication by Sun et al. from 2016.[72] Herein, the role of each component is explained and a plausible mechanism was given. An isoleucine chelated Pd(II) complex catalyses C-H activation of the benzoic acid in *ortho*-position directed by the carboxylic acid functionality. The oxidant, sodium persulfate, generates a Pd(IV) intermediate, which binds *p*-xylene as a ligand. Reductive elimination gives a biphenyl carboxylic acid, which is thought to undergo intramolecular Friedel-Crafts-type

acylation in presence of TfOH. DMSO serves to activate the catalyst and to prevent unreactive palladium black from forming.

1.2 Azafluorenones

1.2.1 Biosynthesis and biological activity

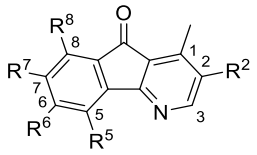
4-Azafluorenone alkaloids are a group of secondary metabolites found mainly in trees or shrubs of the Annonaceae family, the largest subset of the *Magnoliales* order, which are native to tropical and subtropical regions. Structurally, they can be described as fused tryicyclic pyridine analogs of fluorenones. Among annonaceous secondary metabolites, 4-azafluorenones are smaller in number than the more prominent natural products of the acetogenine, diazafluoranthene, protoberberine, azaanthraquinone, (benzyl)isoquinoline, or aporphinoid type[73], the latter from which 4-azafluorenones are hypothesized to be derived biosynthetically (Scheme 9).[74] For the biogenesis of the alkaloids eupolauramine and eupolauridine (**82**), Taylor suggested that the catecholic analogue **79** of the oxoaporphine liriodenine undergoes oxidative extradiol cleavage to the azaanthraquinone carboxylic acid **80**.[74b] The Cavé group considered it likely that from here degradation of the aliphatic side chain and subsequent reduction lead to the azaanthraquinone cleistopholine (**84**) and ultimately the 4-azafluorenone onychine (**86**) upon metalloenzymatically catalysed carbonyl group extrusion analogous to the eupolauridine (**82**) pathway.[74a] With onychine (**86**) representing the simplest member of the 4-azafluorenone group of alkaloids, the question of when and how the hydroxy and methoxy substituents characteristic of its naturally occurring analogs are introduced remains unanswered to this day, although it seems likely to occur at the azaanthraquinone or onychine stage depending on the substitution pattern.[75] Wijeratne et al. proposed the formation of a Favorski-type intermediate **88** from azaanthraquinone precursor **87** that would lead to azafluorenones **89** after ring opening and decarboxylation assuming a prior introduction of phenolic hydroxy substituents.[76]

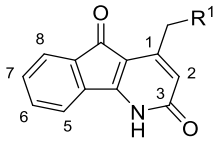


Scheme 9: Postulated biogenisis of eupolauridine (**82**) and onychine[74a] (**86**) as well as congeners.[76]

Onychine (**86**) was first isolated in 1976 from the flowering plant *Onychopetalum amazonicum*[77] and later from the roots or barks of other annonaceous plant species including *Cleistopholis patens*[78], *Polyalthia longifolia*[79], *Unonopsis spectabilis*[80], *Guatteria dielsiana*[81], *Polyalthia debilis*[82], *Polyalthia laui*[83] and *Canaga latifolia*.[84] Its structure was initially determined to be 1-aza-4-methylfluoren-9-one but later revised to 4-aza-1-methylfluoren-9-one by Koyama *et al*. *via* unambiguous synthesis of both structural isomers.[85] In the following years more erroneous structures of the onychine congeners isoursuline[86] (**90**; sometimes referred to as oxylopine) from *Oxandra xylopoides* and 6-methoxyonychine[87] (**91**) from *Guatteria dielsiana* were reported, still referring to the initially reported erroneous structure of onychine (**86**) even years after structural revision had been suggested. With the advent of more sophisticated tools and methods to aid the characterization of chemical compounds, these structural ambiguities have been largely overcome. Renewed isolation efforts have yielded 30 onychine (**86**) analogs from plants of the Annonaceae family to date (Table 1).

Table 1: Overview of known 4-azafluorenone alkaloids. References for their biological sources are given. *Note:* The structure of dielsine[88] (**117**) has been brought into question by the Bracher group's synthetic efforts.[89]





R^1 = H Diesine (**117**)
R^1 = OH Dielsinol (**118**)

Compound	R^2	R^5	R^6	R^7	R^8	Compound	R^2	R^5	R^6	R^7	R^8
onychine[77] (**86**)	H	H	H	H	H	isoursuline[86] (**90**)	H	OH	OMe	H	H
91[81]	H	H	OMe	H	H	**92**[90]	H	H	OH	OMe	OH
polyfothine[91] (**93**)	H	H	OMe	OMe	H	cyathocaline[76] (**94**)	H	OH	OMe	OH	H
95[92]	H	H	H	OMe	H	ursuline[75a] (**96**)	H	OMe	OH	H	H
oncodine[93] (**97**)	H	H	OH	OMe	H	isooncodine[91] (**98**)	H	H	OMe	OH	H
darienine[75a] (**99**)	H	OMe	OMe	OH	H	**100**[94]	H	OMe	OMe	OMe	OMe
101[95]	H	OMe	H	OH	OMe	kinabaline[74a] (**102**)	H	OMe	OH	H	OMe
muniranine[96] (**103**)	H	OMe	OH	OMe	OMe	**104**[97]	H	OH	OMe	OMe	H
penduline[75b] (**105**)	H	H	OH	OH	OMe	macondine[75a] (**106**)	H	H	H	OH	OMe
107[98]	OH	H	H	H	H	**108**[99]	H	OH	H	H	H
109[87]	H	H	OH	H	H	**110**[100]	H	H	H	OH	H
111[87]	H	H	H	H	OH	**112**[101]	H	OH	OMe	H	OH
113[102]	OH	H	H	OH	H	**114**[102]	OMe	H	H	OH	H
115[102]	OMe	H	H	OH	OMe	**116**[87]	OMe	H	OMe	OH	H

Annonaceous extracts have been of great ethnobotanical value to indigenous cultures in tropical regions as a cure for various pathogenic conditions for centuries[73, 103], urging the elucidation of the pharmalogical properties of their individual components. The majority of the 4-azafluorenone alkaloids known today have yet to be thoroughly investigated in pharmalogical studies. Yet, some of those that have exhibited a wide array of biological activities including antifungal, antiproliferative, and antibacterial effects against multiple strains that make them attractive scaffolds for drug development.[104]

Naturally, onychine (**86**) is among the more well-studied 4-azafluorenone alkaloids. Weak to moderate antimicrobial activity against common representatives for Gram-positive and Gram-negative bacteria, yeasts, and filamentous fungi were observed (MIC = 50-100 mg/mL).[105] The compound reportedly also exhibits potent anticandidal properties (MIC = 3.1 μg/mL against *Candida albicans*)[78, 106] and inhibits proliferation of vascular smooth muscle cells[107]

as well as activation of caspase-3 during oxidative stress-induced apoptosis in ECV304 endothelial cells, which may have a beneficial effect on endothelial injury.[108]

Isoursuline (**90**) has potential as an antimalarial agent showing IC_{50} values of 9.9 and 11.4 µM against two different strains of the parasite *P. falciparum* 3D7 and Dd2.[101]

6,8-Dihydroxy-7-methoxyonychine (**92**) exhibits potent cytotoxic activities with IC_{50} values in the range of 2.6-3.6 µg/mL for the human lung cancer cell lines A549, GLC4 and GLC4/Adr. The compound was hereby not recognized by the human MRP1 protein which is involved in transporting pharmalogically active substances out of the cell and thus contributes to conferring multidrug resistance to tumorous cells. It also displays potent antitubercular activity, inhibiting *M. tuberculosis* with an MIC value of 0.8 µg/mL, equal to that of ofloxacin, which was used as a positive control.[109] Lastly, it was also reported to induce caspase-8 and caspase-9-mediated apoptosis in human cancer cells.[110]

To a lesser degree, DNA damaging and DNA modifying effects have also been reported for polyfothine[111] (**93**), cyathocaline[76] (**94**), and an isomeric mixture of 6-methoxy and 7-methoxyonychine[111] (**91**, **95**), respectively. A review of onychine (**86**) and its congeners covering biological activites and synthetic methods has been published recently.[104]

The promising pharmacological properties of onychine (**86**) and its congeners naturally spurred the development of synthetic analogs, among which derivatives with herbicdal[112], antiproliferative[113], antiprotozoal[114], antimicrobial[115] properties have been synthesized.

For example, Marquise and coworkers prepared a library of substituted 4-azafluorenones with many compounds displaying potent biological activities.[113a] Nearly all compounds tested displayed antifungal activity higher than the positive control nystatin against *C. albicans*, while displaying moderate to high antibacterial activity against *E. coli* and *S. aureus*. Compound **119** exhibits potent antimalarial properties against *P. falciparum* while showing no cytotoxicity at 10 µM (Figure 3). Compound **120** containing a benzothienyl ring showed strong antiproliferate activity.

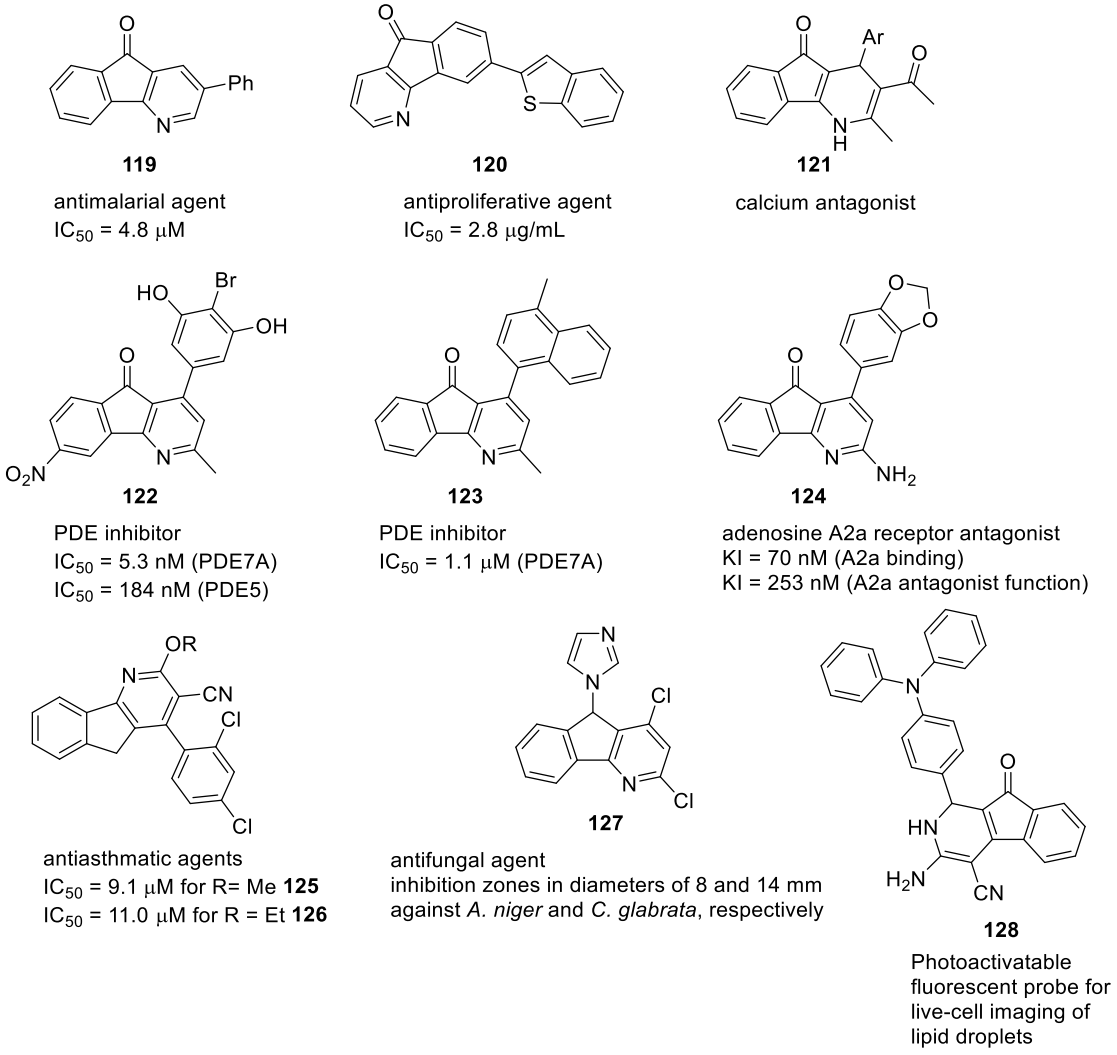


Figure 3: Selection of biologically active synthetic azafluorenone derived compounds.

A patent was filed by Ortho-McNeil Pharmaceutical detailing the preparation of synthetic 4-azafluorenonderivatives as potential adenosine A2a receptor antagonists and phosphodiesterase inhibitors for the treatment of neurodegenerative and movement disorders.[116] Some compounds like **122** reached the single-digit nM range or showed selectivity towards one of three tested phosphodiesterases families (PDE7A, PDE4, PDE5) like **123** towards PDE7A while compound **124** proved a potent and selective A2a antagonist.

The Bracher group prepared an onychine derivative **127** bearing a moiety characteristic of the antifungal azole eberconazole that, while only moderate in its antifungal activity, did not inhibit ergosterol biosynthesis like other azoles.[117]

Furthermore, over several studies select derivatives have been shown to possess potent antiasthmatic[118] or antithrombic[119] characteristics as well as potential as calcium antagonists[120] and carbonic anhydrase inhibitors[121], often accompanied by excellent pharmacokinetic properties and potency exceeding the standard reference substances used.

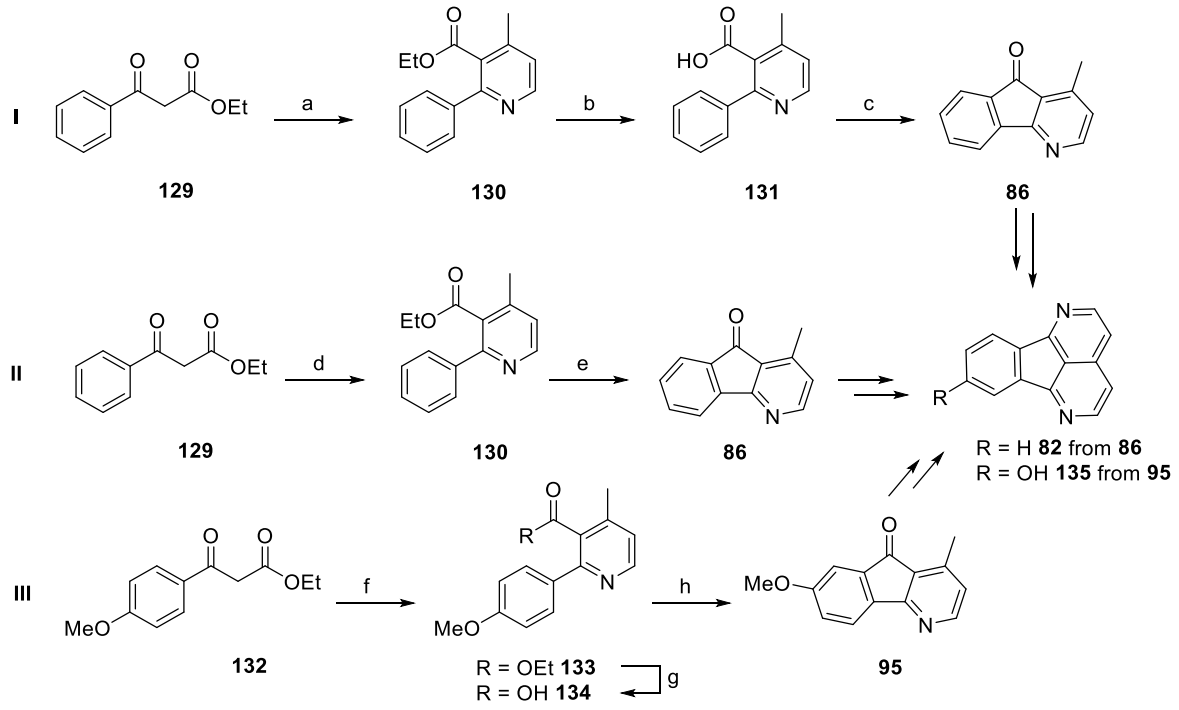
Synthetic azafluorenone derivatives have also attracted great interest for their optical and photo-physical properties. For example, a patent was filed by Kosuge et al. detailing the invention of an organic light-emitting device (OLED) featuring a fluorescent electron transport layer between the electrodes containing bulky polycyclic derivatives of 4-azafluorenone.[122] Meanwhile, compound **128** has been developed as one of three 2-dihydroazafluorenone derived photoactivatable, non-selfquenching, bioluminescent probes for the live-cell imaging of lipid droplets that can be photooxidized with high efficiency to give their activated 2-azafluorenone counterparts.[123]

1.2.2 Synthesis of 4-azafluorenones and 4-azafluorenone-type alkaloids

Approaches towards the 1-methyl-4-azafluorene skeleton naturally resemble those discussed for fluorenone synthesis due to their structural similarity. Other noteworthy methods include key steps such as intramolecular aza-Wittig reaction[124], Pummerer cycloaddition cascade[125], or hetero Diels-Alder cycloaddition[126], which lead towards the azafluorene skeleton and require subsequent oxidation. In the same vein, a variety of new methods for the preparation of commonly employed intermediates have been developed. For 2-arylnicotinates, this includes arylation of 2-halopyridine *N*-oxides with Grignard reagents[127], tandem one-pot reaction using a Blaise intermediate and 1,3-enynes[128], $FeCl_3$-mediated condensation of α-phenylenamino esters and enones[129], thermal cyclization of *N*-propargyl enamines[130] or aza-Wittig reaction of *N*-vinylic phosphazenes with α,β-unsaturated aldehydes and subsequent [2+2] cycloaddition-cycloreversion sequence[131]. A functionally analogous (benzylsulfonyl)-tetrahydropyridine carboxylate has been prepared *via* aza-Morita-Baylis-Hillman reaction.[132] Aside from Friedel-Crafts-type cyclization in strongly acidic media, arylnicotinates can also be further transformed to the corresponding nicotinaldehydes, 3-hydroxymethyl-2-phenylpyridines and 2-(pyridinyl)benzylalcohols, which have been cyclized to various 1-, 2-, 3-, and 4-azafluorenones with *tert*-butyl hydroperoxide (TBHP).[133]

4-Azafluorenones also have synthetic importance as intermediates of related polycyclic aromatic alkaloids. In fact, onychine (**86**) was first reported by the Taylor group in 1975, not as a newly discovered alkaloid, but as an intermediate for the first total synthesis of the diazafluoranthene eupolauridine (**82**, Scheme 10).[134] Hereby, ethyl benzoylacetate (**129**) was condensed with crotonaldehyde and concentrated ammonia at room temperature. Alkaline hydrolysis of the resulting nicotinate ester **130** to the corresponding acid **131** and subsequent cyclization with polyphosphoric acid (PPA) gave the natural product (**86**, **I**). This route was later optimized by Franz Bracher resulting in a more efficient two-step synthesis (**II**).[135] Pan and coworkers attempted preparation of 7-methoxyonychine (**95**, **III**) as an intermediate towards the alkaloid 8-hydroxyeupolauridine (**135**) with a similar protocol but found that the methoxylated nicotinate ester **133** reacted poorly with PPA. Instead, cyclization was

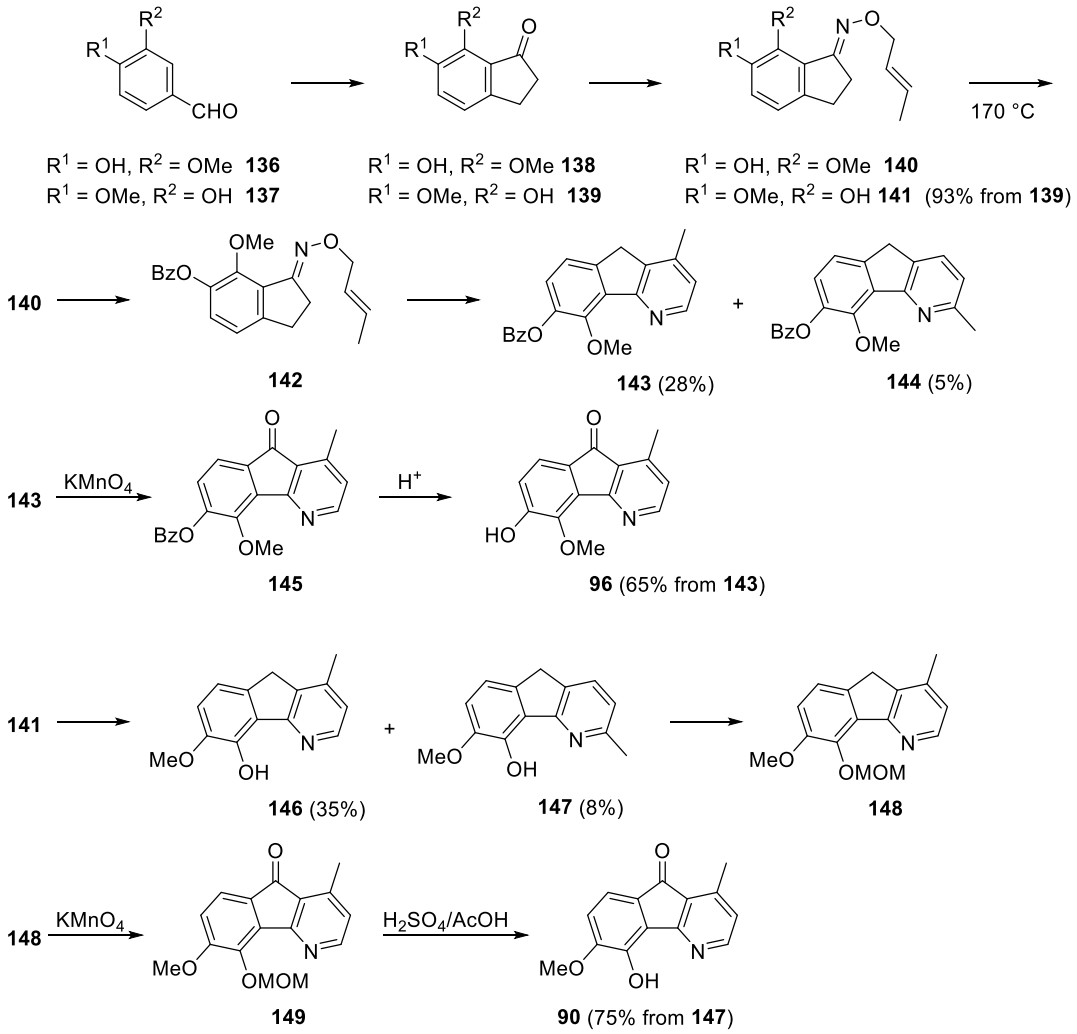
accomplished by prior alkaline hydrolysis to the corresponding carboxylic acid **134**, *in situ* conversion to the acyl chloride and subsequent reaction with $AlCl_3$.[136]



Scheme 10: First reported total synthesis of onychine (**86**) by the Taylor group.[134] (**I**), modified synthesis by Bracher[135] (**II**) and preparation of 7-methoxyonychine (**95**) by Pan et al.[136] (**III**). Conditions: a) aqueous conc. NH_3, crotonaldehyde, EtOH, 0 °C ⟶ rt, overnight, 10 %; b) 40% aqueous KOH, EtOH, reflux, overnight, 80%; c) PPA, 130 °C, 3 h, 92%; d) NaH, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100–110°C, 90 min, 43%; e) PPA, 130 °C, 4 h, 81%; f) NaH, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 90 min, 32%; g) 40% aqueous NaOH, reflux, overnight; 66%; h) first $SOCl_2$, 24 h, reflux; then $AlCl_3$, chlorobenzene, reflux, overnight, 25% over two steps.

More classic synthetic approaches to 4-azafluorenone alkaloid synthesis include oxidative thermal rearrangement of indanoneoxime *O*-crotyl ethers[137], catalytic dehydrocyclization of 3,4-dimethyl-2-phenlpyridine to the 4-azafluorene followed by oxidation[138], and Pd(0)-catalyzed cross-coupling of arylboronic acids with 2-halopyridines for the preparation of nicotinates prior to PPA-mediated cyclization.[139] However, these and similar methods were not ideal for the synthesis of substituted 4-azafluorenones as they would often require harsh conditions, give complex isomeric mixtures for asymmetrically substituted substrates and lacked flexibility as starting materials with more complex substitution patterns were not readily available.[140] For example, Koyama et al. reported the first total synthesis of ursuline (**96**) and isoursuline (**90**, Scheme 11).[140b] Therein the respective indanones **138** and **139** were treated with crotylhydyroxylamine to afford the oxime *O*-allyl ethers **140** and **141**. Thermolysis at 170 °C afforded a mixture of 1- and 3-methyl-4-azafluorenes, followed or preceeding protection of the free phenolic groups as MOM ethers or benzoyl esters. While the desired 1-methyl derivatives were furnished as the major products, the yields were relatively low (28% for **143**, 35% for **146**) and the starting materials were not completely consumed despite the harsh

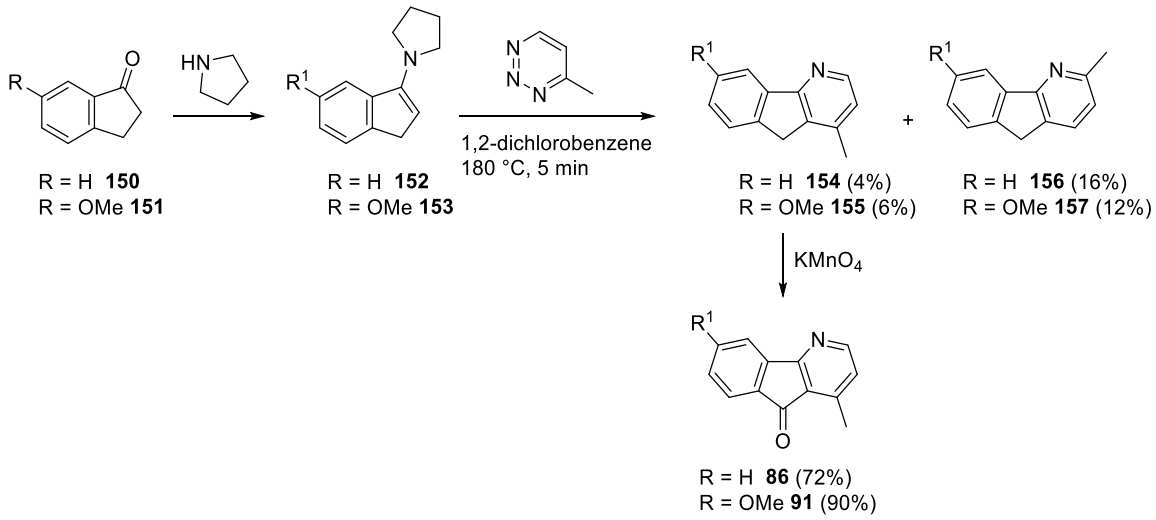
reaction conditions (20% of **142** and 18% of **141** recovered). The 1-methyl derivatives **143** and **148** were then oxidized with $KMnO_4$ and deprotected to give the natural products.



Scheme 11: First total synthesis of ursuline (**96**) and isoursuline (**90**) by Koyama et al.[140b] *Note*: The exact reaction conditions were specified only partially.

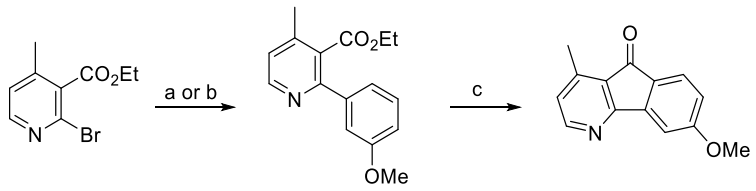
Similar synthesis routes have been employed by the same group as well as Cavé's group to prepare monomethoxylated C-5, C-6, C-7, and C-8 derivatives of onychine (**86**) by thermolysis of appropriately substituted methoxyindanone oximes.[141] Cavé's group further prepared the corresponding hydroxy derivatives, all of which are natural products, *via O*-demethylation of the methoxyonychines with concentrated hydrobromic acid. In a separate publication Cavé's group also accomplished the total synthesis of the alkaloids polyfothine (**93**), oncodine (**97**) and isooncodine (**98**) with this methodology.[93] Later, an improved thermolysis protocol was developed by Koyama et al., wherein addition of the lewis acid $BF_3{\cdot}Et_2O$ facilitated near regioselective rearrangement of the indanoneoxime *O*-crotyl ethers to the desired 1-methyl-4-azafluorene intermediates.[142] This method was applied for the total synthesis of the onychine (**86**) and polyfothine (**93**).

Another method for the conversion of 1-indanones to 1-methyl-4-azafluorenes was reported by Okatani et al.[143] Pyrrolidine enamines **152** and **153** generated from 1-indanones **150** and **151**, respectively, were hereby reacted with 4-methyl-1,2,3-triazine in 1,2-dichlorobenzene at 150–160 °C in a Diels-Alder reaction and gave an isomeric mixture of 1- and 3-methyl-4-azafluorenes **154**–**157**. The yields, however, were noticeably lower compared to those reported for thermolysis of indanoneoxime *O*-crotyl ethers with yields of only 4% (R = H) and 6% (R = OMe) reported for the desired 1-methyl isomers **154** and **155**. The respective 1-methyl-4-azafluorenes were then oxidized with $KMnO_4$ to give onychine (**86**) and 6-methoxyonychine (**91**).



Scheme 12: Totlal synthesis of onychine (**86**) and 6-methoxyonychine (**91**) *via* Diels-Alder reaction of pyrrolidine enamines of 1-indanones with 4-methyl-1,2,3-triazine by Okatani et al.[143] *Note*: The exact reaction conditions were specified only partially.

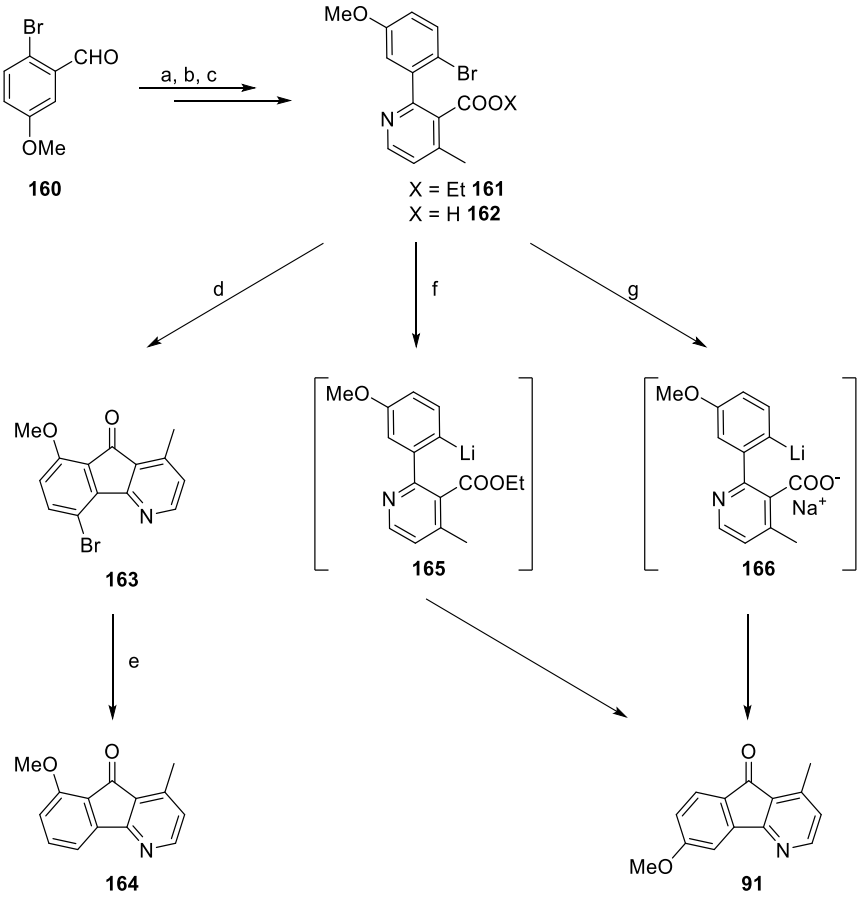
Another synthesis of 6-methoxyonychine (**91**) reported by Snieckus' group, also applied for onychine (**86**), reacted PPA directly with the nicotinate esters rather than the nicotinic acids (Scheme 13).[139] The arylnicotinate ester **159** was prepared *via* Suzuki coupling and Stille-coupling for the first time. The PPA-mediated cyclization seemed to proceed regioselectively as formation of 8-methoxyonychine was not mentioned. Tagawa and coworkers similarly prepared arylnicotinic esters *via* Suzuki coupling for the synthesis of polyfothine (**93**) and 7-methoxyonychine (**95**), prior to hydrolysis and cyclization with Eaton's reagent (10 wt% P_4O_{10} solution in methanesulfonic acid).[144] It was hereby also noted, that nicotinic acids furnishing methoxy residues in *ortho*-position on the benzene ring undergo lactonization when treated with Eaton's reagent and the respective coumarin derivatives were prepared thusly.



158 **159** **91**

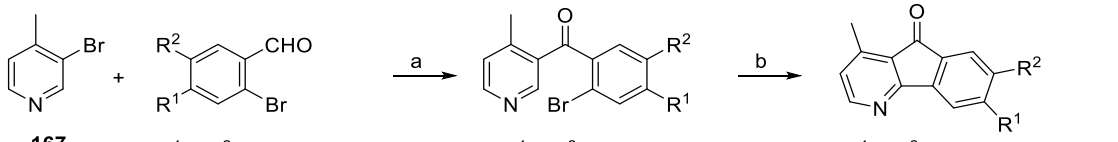
Scheme 13: Total synthesis of 6-methoxyonychine (**91**) by the Snieckus' group.[139] Conditions: a) 3-methoxyphenyboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, THF, reflux, 24 h, 82%; b) 3-trimethylstannylanisole, $Pd(PPh_3)_4$, THF, reflux, 24 h, 95%, c) PPA, 220 °C, 2 h, 80%.

The first unambigiously regioselective synthesis of substituted onychine derivatives was developed by Bracher for the preparation of the alkaloid 6-methoxyonychine (**91**) and its unnatural regioisomer 8-methoxyonychine (**164**, Scheme 14).[145] The key idea to controlling the regioselectivity during cyclization of arylnicotic acid **162** was the prior introduction of a bromide substituent at C-2' which can then be converted to either isomer by choice of the appropriate reaction conditions. PPA-mediated cyclization of nicotinic acid **162** with one position blocked ultimately gives 8-methoxyonychine (**164**) after subsequent bromide removal *via* catalytic hydrogenation. To access 6-methoxyonychine (**91**), arylnicotinic ester **161** is directly treated with 1.5 equivalents of *n*-BuLi at very low temperatures. The lithiated species **165** generated *via* halogen-metal exchange then furnishes the natural product in a Parham cyclization. Alternatively, nicotinate ester **161** is converted to the organometallic lithium species **166** with 1.0 equivalents of *n*-BuLi only after previous alkaline ester hydrolysis with NaH, which then cyclizes to give desired product.



Scheme 14: Regioselective total synthesis of 6-methoxyonychine (**91**) and 8-methoxyonychine (**164**) by Bracher.[145] Conditions: a) ethyl diazoacetate, $SnCl_2$, DCM, rt, 2 h, 66%; b) benzyltrimethylammonium hydroxide, crotonaldehyde, rt, 30 min, then hydroxylammonium chloride, AcOH, reflux, 30 min, 30%; c) KOH, EtOH/H_2O, reflux, 4 h, 82%; d) PPA, 130 °C, 30 min, 79%; e) H_2/Raney nickel, MeOH, EtOAc, NaOAc, rt, 15 min, 86%; f) *n*-BuLi (1.5 equiv.), THF, -100 °C ⟶ -78 °C, 30%; g) NaH, THF, then *n*-BuLi (1.0 equiv.), -78 °C, 45 min, 40%.

Finally, the Kraus group developed a strategically distinct methodology (Scheme 15).[146] Hereby, 3-bromo-4-picoline (**167**) is converted to the organolithium compound *in situ* by treatment with *n*-BuLi and subsequently reacted with appropriately substituted 2-bromobenzaldehydes **160**, **168** and **169**. The resulting crude secondary alcohols are further oxidized with MnO_2 to give the azabenzophenones **170-172**. Ring closure is achieved *via* a Pd(0)-catalyzed Heck reaction. The alkaloids onychine (**86**), polyfothine (**91**) and 7-methoxyonychine (**95**) were prepared with this methodology. The authors proclaim that the flexibility of their method enables the preparation of a variety of azafluorenone analogues but have not published follow-up studies to date.



$R^1 = R^2 = H$ **168**
$R^1 = R^2 = OMe$ **169**
$R^1 = H, R^2 = OMe$ **160**

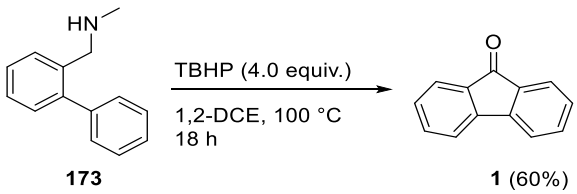
$R^1 = R^2 = H$ **170** (68%)
$R^1 = R^2 = OMe$ **171** (86%)
$R^1 = H, R^2 = OMe$ **172** (80%)

$R^1 = R^2 = H$ **86** (53%)
$R^1 = R^2 = OMe$ **91** (47%)
$R^1 = H, R^2 = OMe$ **95** (50%)

Scheme 15: Total synthesis of onychine (**86**) and onychine derivatives by the Kraus group.[146] Conditions: a) *n*-BuLi, THF, -100 °C, 10 min, then **168**, **169** or **160**, -78 °C ⟶ rt, 8 h; ii) MnO_2, benzene, reflux, 18 h; b) $Pd(OAc)_2$, TBAC, base, DMF, heated to completion.

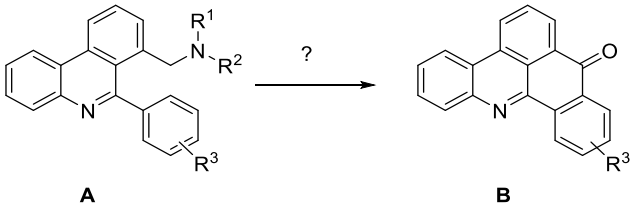
2 Objectives

In direct continuation of my Master's thesis[147], the method devised for the synthesis of fluorenones from *N*-methyl-2-(aminomethyl)biphenyls (Scheme 16) was to be further refined, characterized with additional examples and applied for the synthesis of yet-to-be synthesized fluorenone-type natural products. While similar TBHP-mediated cyclizations of aldehydes and alcohols were known[148], the reaction with amines had yet to be described.



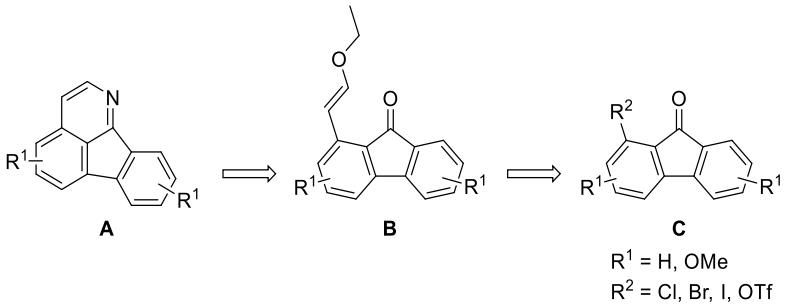
Scheme 16: Best result for the cyclization of *N*-substituted 2-phenyl benzylamines with various reagents, conducted during my Master's thesis.[147]

The initial objective set during my Master's thesis emerged from the Bracher group's alumni Alois Plodek's[149] and Benedikt Melzer's[150] research on pyridoacridines: A method for an efficient construction of the pyridoacridine skeleton was sought after, envisioned *via* ring-closure and transformation of the *N*,*N*-dialkylbenzylamine moiety of intermediate **A** to give cyclic ketone **B**, ideally in a single cascade reaction (Scheme 17).



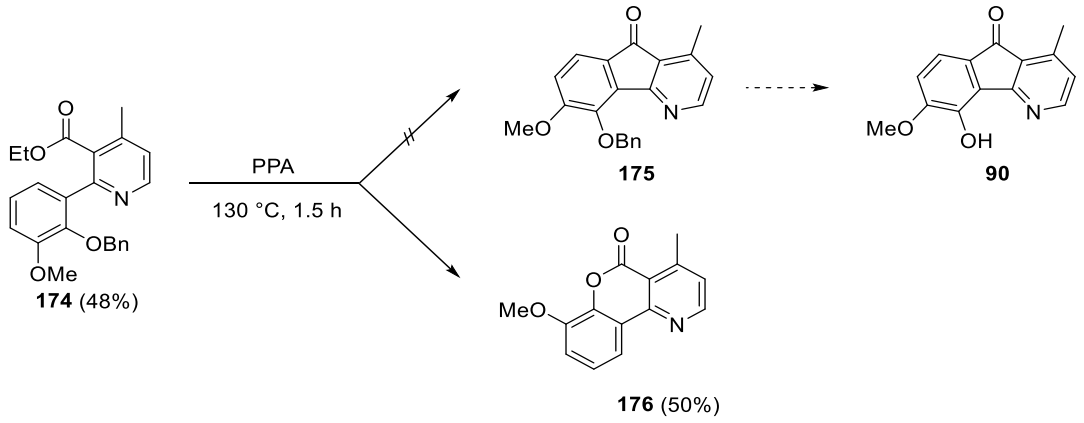
Scheme 17: Hypothetical one-step oxidative ring closure of a benzylamine moiety for the construction of a cyclic ketone moiety during pyridoacridine synthesis.

The TBHP-mediated cyclization, however, performed poorly with tertiary amines and amides, making it most likely unsuitable for the ring closure described above. Instead, the goal was shifted towards the total synthesis of azafluoranthene alkaloids (Scheme 18). These were envisioned to be accessible *via* a key intermediate fluorenones **C**, building on the previously devised method for the synthesis thereof. Installation of a leaving group suitable for cross coupling with ethoxyvinylboronate at C-1 to form intermediates **B**, and subsequent intramolecular condensation with ammonium aceate would then lead to the desired azafluoranthenes **A**.



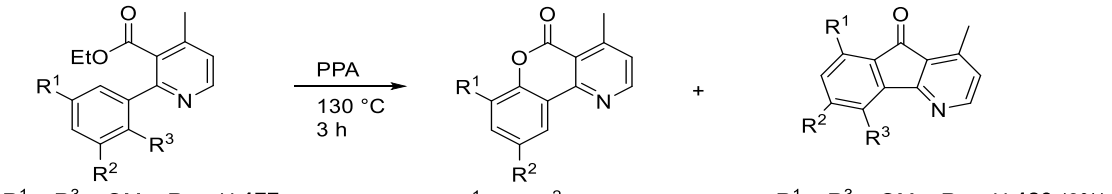
Scheme 18: Retrosynthesis of azafluoranthenes **A**.

The TBHP-mediated cyclization was to also be employed for the synthesis of structurally related 4-azafluorenones, which had proved challenging in previous synthetic efforts made by the Bracher group. As part of his Habilitation thesis[151], Franz Bracher developed a method for the synthesis of onychine (**86**).[135] At the time, two research groups independently isolated an azafluorenone alkaloid by the name of isoursuline from *Oxandra xylopiodes*[87] and *Unoopsis spectabilis*[80], respectively. Both the Slatkin group and the Cavé group proposed the same structure for the alkaloid, only differing in two substituents at the phenyl ring from onychine (**86**). However, the spectroscopic data reported for these two compounds differed significantly. This prompted an investigation to determine which of the two isolated alkaloids reported had the proposed structure of isoursuline (**90**) by unambiguous total synthesis (Scheme 19). However, thermal cyclization of nicotinate ester intermediate **174** with PPA unexpectedly gave the lactone **176** instead of the desired azafluorenone **175**.



Scheme 19: Attempted total synthesis of isoursuline (**90**) reported by Franz Bracher.[151]

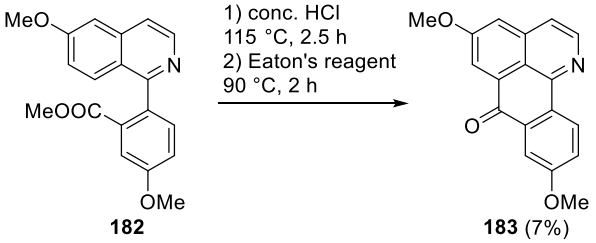
Lactonizations of this nature with arylnicotinate esters bearing alkoxy residues in *ortho*-position of the benzenoid ring had been previously reported by Zhang et al. for the PPA-mediated cyclization of two nicotinate esters **177** and **178** (Scheme 20).[87] Both reactions gave the corresponding lactones **179** and **176** as the major products, although formation of small amounts of azafluorenones **180** and **181** was observed. This is reminiscent of the lactonizations discussed for fluorenone natural product synthesis (Section 1.1.2).



Scheme 20: PPA-mediated cyclization of 2'-oxygenated nicotinate esters **177** and **178** reported by Zhang et al.[87]

Evidently, 4-azafluorenones bearing alkoxy residues at C-5 are virtually inaccessible *via* thermal cyclization in strongly acidic media. With many 4-azafluorenone alkaloids out of synthetic reach with conventional methods, this issue was to be circumvented by application of the developed TBHP-mediated cyclization for the synthesis of structurally related 4-azafluorenone natural products.

One of the isooxoaporphine alkaloids for which Benedikt Melzer developed a total synthesis during his PhD thesis was bianfugecine (**183**, Scheme 21).[150]

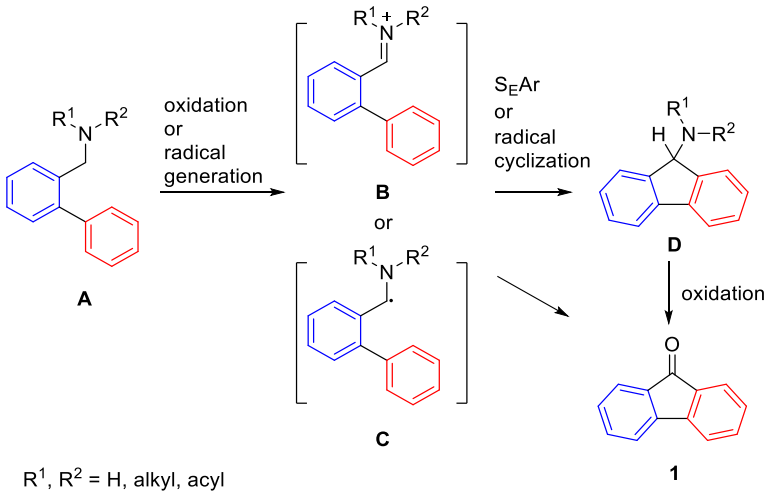


Scheme 21: Cyclization of intermediate **182** to bianfugecine (**183**).

Unlike other related target compounds, the final cyclization step for bianfugecine (**183**) proved to be challenging. Friedel-Crafts-type cyclization methods of ester **182** with triflic acid, the carboxylic acid with TFAA and the acyl chloride with $AlCl_3$ failed. Only acidic hydrolysis of ester **182** prior to reaction with Eaton's reagent (10 wt% P_4O_{10} in methanesulfonic acid) furnished the desired product with a low yield of 7%. As part of a side-project, it was to be investigated whether the yield of this step could be improved with the TBHP-mediated cyclization.

3 Summary of my Master's thesis

The following considerations for the development of a new method for the intramolecular oxidative cyclization of benzylamines were made using 2-phenylbenzylamines as model compounds. Starting from aminomethylated biphenyl **A**, the formation of a reactive iminium ion key intermediate **B** or radical intermediate **C** was hypothesized to be generated *via* oxidation (Scheme 22). The iminium ion would then form a new five-membered ring *via* intramolecular ring closure following either a S_EAr or radical mechanism. This would furnish aminofluorene **D**, which is in turn further oxidized to fluorenone (**1**) by either excess oxidant or driven by the present reaction conditions. The reaction stopping at the stage of aminofluorene **D** would necessitate an additional, separate oxidation step. While less preferable, this result was also deemed acceptable. Residues R^1 and R^2 were envisioned to stabilize the hypothetical benzyl iminium ion or radical intermediate, thereby promoting the generation thereof through electron donating +*I*-effects of primarily alkyl groups. However, in order to gain a greater understanding of the potential reaction scope, residues with electron withdrawing effects such as acyls and carbamates were also included.

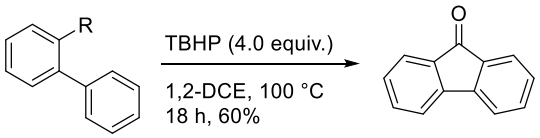


Scheme 22: Hypothetical oxidative cyclization of aminomethylated biphenyl **A** *via* S_EAr or radical pathway to fluorenone (**1**).

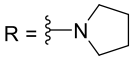
Based on these preliminary considerations, a systematic study on the cyclization potential of aminomethylated biaryls and related compounds was launched.[147] A wide range of reagents reported in the literature in the context of benzylamine oxidation were screened and evaluated *via* thin-layer chromatography (TLC) for their suitability in this reaction including cerium salts, hypervalent iodine compounds, nitroxyls, peroxides, persulfates, silver(I) salts, tetrahalomethanes and triphenylcarbenium ions. Ultimately, among all oxidants tested, only aqueous *tert*-butyl hydroperoxide proved effective in furnishing the desired product fluorenone (**1**) in an acceptable yield, starting from either the primary amine **184** or *N*-methyl derivative

173 (Scheme 23). Out of all the other nitrogen-containing functional groups tested, including a tertiary amine, secondary and tertiary amide, nitrile, and carbamate, only the secondary amide **185** and tertiary amine **189** gave fluorenone (**1**) after reaction with TBHP, albeit in drastically lower yields. Attempts at reaction optimization, such as altering the reaction temperature, equivalents of TBHP employed and the use of different solvents or additives including $Pd(OAc)_2$, tetra-*n*-butylammonium iodide (TBAI), $Cu(OAc)_2$, AgF, $NiCl_2 \cdot 6\ H_2O$, and $Ni(OAc)_2 \cdot 4\ H_2O$ in different equivalents were unrewarding and the initial conditions (solvent: 1,2-DCE, 100 °C, 18 h) proved most effective. The scope of additives was expanded upon after completion of my Master's thesis ($Pd(OAc)_2/K_2CO_3$, TFA, Cu(acac), DMF/AcOH, TBAI/DMF/AcOH, CAN/MeCN, CuBr/DMSO, I_2/DMSO), which however did also not yield any noteworthy results. Depending on the substrate however, an increased reaction time can be beneficial.

Interestingly, the yield of fluorenone (**1**) furnished by primary amine **184** differed greatly depending on what kind of solvent TBHP was diluted in. Reaction with aqueous TBHP (62%) gave a significantly better yield than reaction with TBHP in *n*-decane (22%) despite resulting in a heterogeneous reaction mixture in case of the former. Meanwhile, isoelectronic alcohol **186** gave the exact opposite results: an acceptable yield with TBHP in *n*-decane (60%) and a low yield with aqueous TBHP (26%). This suggests the involvement of water in the cyclization mechanism of amines.



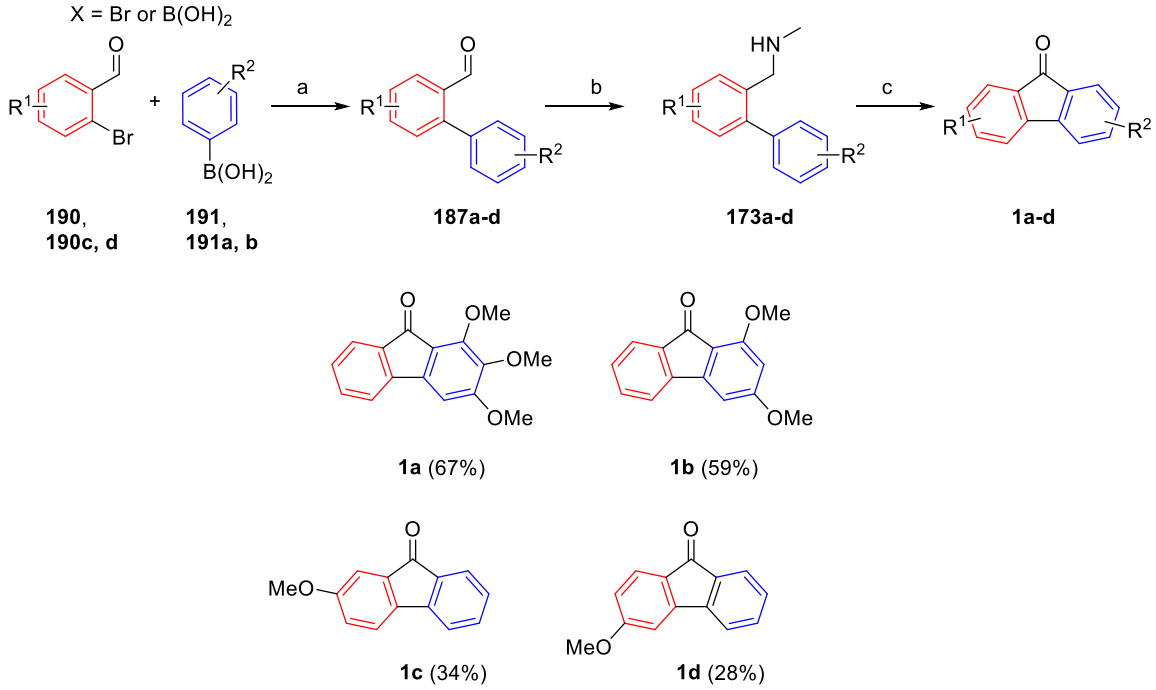
1

R = -CH_2NHCH_3 **173**	60%[a]
R = -CH_2NH_2 **184**	62%[a], 22%[b]
R = -CH_2-NH-$COCH_3$ **185**	20%[a]
R = -CH_2-OH **186**	26%[a], 60%[b]
R = -CHO **187**	25%[a], 26%[b]
R = -CN **188**	0%
R =  **189**	13%[a]

Scheme 23: Cyclization of biphenyls with different reactive moieties in *ortho*-position. [a]reaction performed with aqueous TBHP (70%); [b]reaction performed with TBHP in *n*-decane (5.5 M).

Having determined the most suitable reaction conditions and functional groups within the allotted time frame of the Master's thesis, four model fluorenones **1a**-**1d** were synthesized by cyclization of *N*-methylamines **173a**-**173d** (Scheme 24). The respective *N*-methylamines **173a**-**173d** were accessible through a two-step synthesis consisting of Suzuki coupling of suitable 2-bromoaldehydes **190**, **190c** and **190d** as well as boronic acids **191**, **191a** and **191b** followed by reductive amination of the biphenyl-2-carboxaldehydes **187a**-**187d** with methylamine. Noticeably, the yield of the TBHP-mediated cyclization seemed to favor methoxy residues on

the radical accepting ring (67% and 59%), while methoxy residues on the ring bearing the benzylamine moiety led to a significant yield decrease (34% and 28%).



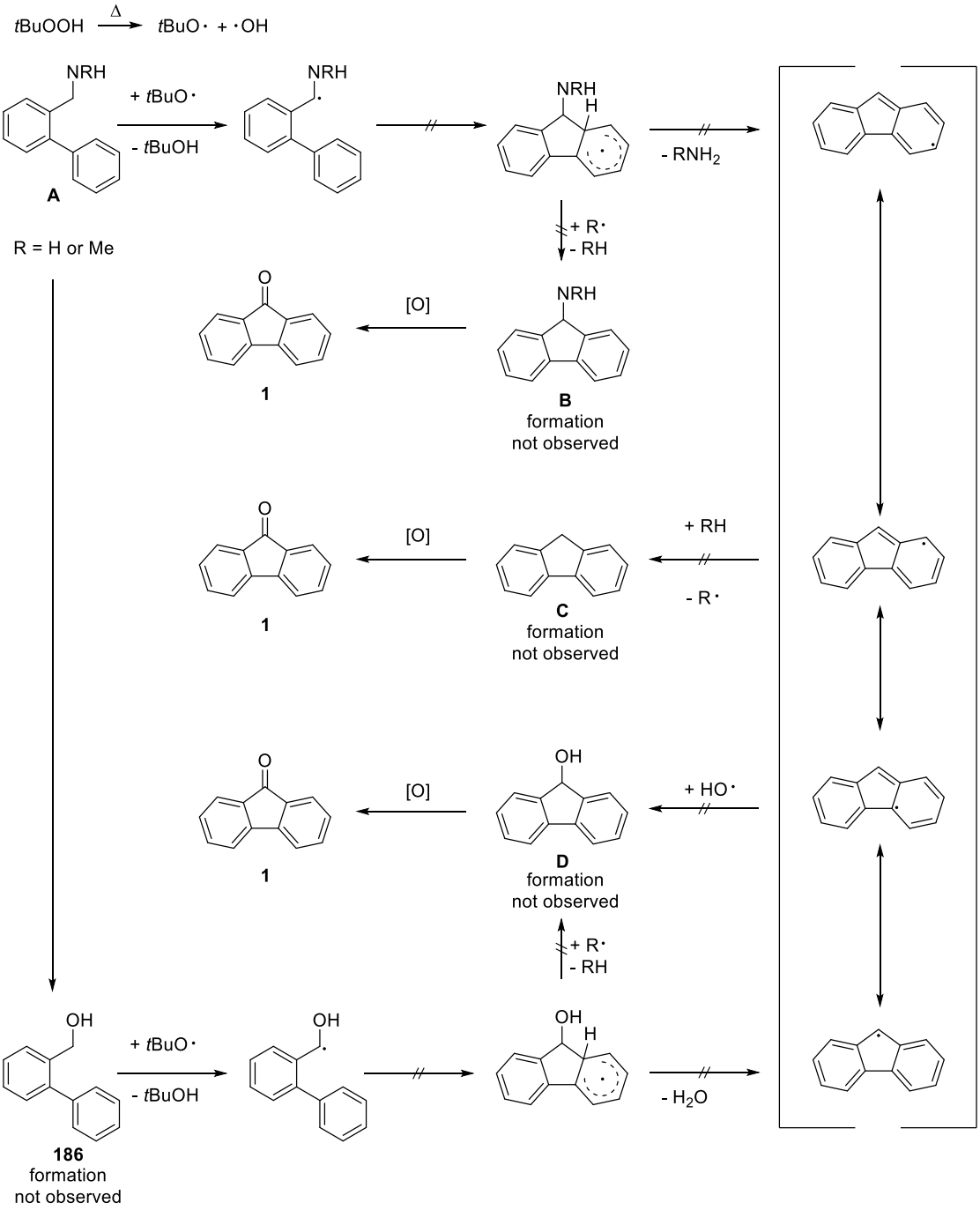
Scheme 24: Substrate scope and yield for oxidative cyclization of *N*-methyl-2-(aminomethyl)biphenyls bearing methoxy residues. Conditions a) $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O, 100 °C, 18 h, 76–96%; b) $MeNH_2$, $NaBH_4$, DCM, rt, 18 h, 62–78%; c) $TBHP_{aq}$, 1,2-DCE, 100 °C, 18 h (yields in parentheses).

Although the major projects discussed in this thesis are intricately connected with the research described up to this point, most of it was conducted during my Master's thesis, necessitating discussion thereof to some degree. Some of the functional group compatibilities with the TBHP-mediated cyclization presented here were investigated by then-student Lukas Zeisel shortly thereafter. For the sake of brevity, further details are omitted. Unless explicitly stated otherwise, all experiments described starting from Section 4 were conducted as part of the PhD thesis.

3.1 Mechanistic considerations:

The following observations were made during experiments pertaining to the underlying mechanism of the TBHP-mediated cyclization of 2-phenylbenzylamines. First off, the reaction proceeded more smoothly in aqueous TBHP (70%) than in water-free TBHP (commercially available as ~5.5 M dilutions in *n*-nonane or *n*-decane), suggesting that water takes part in the reaction. Interestingly, adding water to a reaction mixture with TBHP in *n*-decane did not result in a yield increase. Performing the reaction under nitrogen atmosphere did not affect the reaction yield despite it being a radical reaction. Presumably, the intramolecular nature of the reaction and close vicinity of reaction sites prevents side-reaction with oxygen from occurring in noticeable frequency. As neither the aminofluorene **B** nor fluorene **C** intermediates were

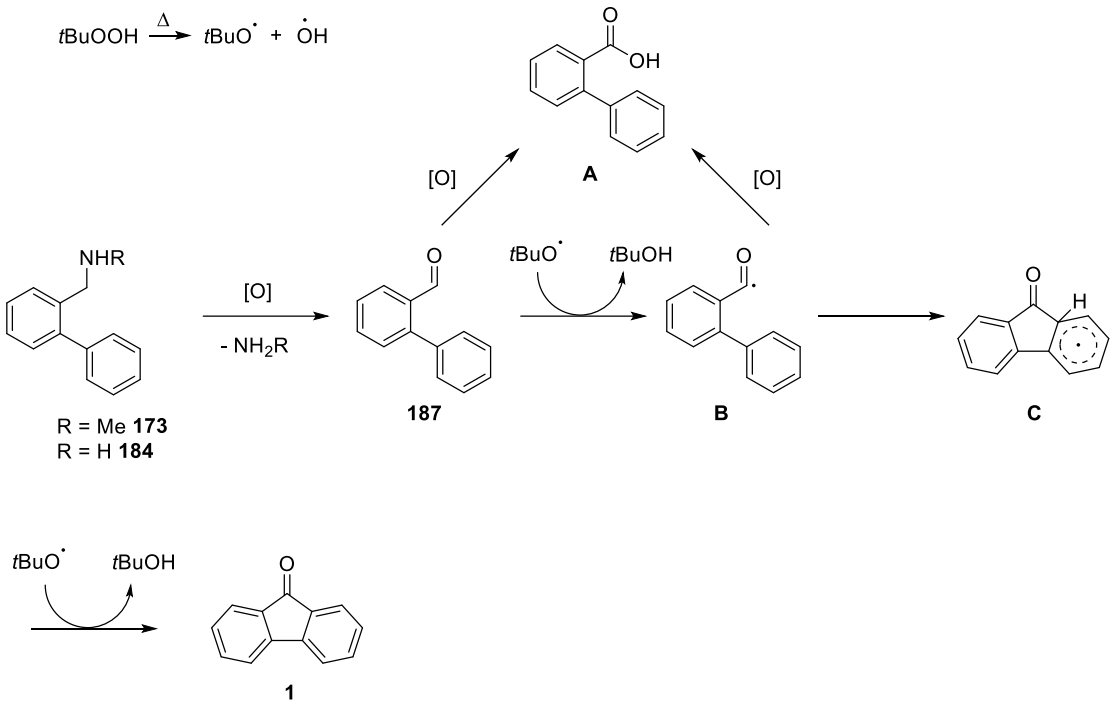
observed *via* TLC or GC-MS reaction control experiments, it is reasonable to assume that the amine functional group is eliminated prior to cyclization (Scheme 25). Furthermore, formation of fluorenol **D** was also not observed, indicating that it is not the benzyl alcohol **186**, but the benzaldehyde **187** that is cyclized. As these hypothetical intermediates (aminofluorene **B**, fluorene **C** and fluorenol **D**) are stable compounds, it is assumed that they are not reactive to the degree that their formation would not be observable even in small traces *via* GC-MS and TLC-MS.



Scheme 25: Preclusion of reaction pathways for the TBHP-mediated radical cyclization of 2-(aminomethyl)biphenyls based on the absence of certain intermediates.

Based on these considerations, pathways that do not feature the benzaldehyde **187** as the key intermediate prior to cyclization were ruled out. In a separate experiment, reaction of 2-phenylbenzaldehyde (**187**) with both aqueous and TBHP in *n*-decane only yielded 25% and 26% fluorenone respectively (Scheme 23). In the literature this reaction synthesis has been reported to proceed with a yield of 62% by the Singh group with benzene as the solvent.[148] However, we were unable to reproduce this result with 1,2-DCE. Moreover, adding further equivalents of aqueous TBHP to a mixture of fluorenone and aldehyde did not noticeably increase the yield. Perhaps aqueous TBHP (in contrast to water-free TBHP) promotes the oxidation of the benzylamine to the benzaldehyde, although it is unclear if water directly takes part in the mechanism. Studies indicate that water may lower the activation barrier for the radical cyclization owing to its solvent effect, as has been previously reported for the radical synthesis of lactones.[152] Finally, the benzaldehyde **187** and the benzoic acid were observed as frequent side products. To fully understand the underlying mechanism, a more detailed investigation is required. For example, isotopically labeled TBHP or TBHP diluted in D_2O could be used to elucidate the origin of the carbonyl oxygen of fluorenone (**1**). However, based on the observations made within the project frame allotted to mechanistic considerations, only a tentative mechanism for the TBHP-promoted oxidative cyclization of amines **173** and **184** was proposed (Scheme 26).

Primary or secondary benzyl amines **173** and **184** are first oxidized by TBHP to benzaldehyde **187**. From here, the benzaldehyde **187** can either be further oxidized to give commonly observed side product benzoic acid **A** or generate an acyl radical **B** through proton abstraction by a free radical generated through homolytic cleavage of the peroxide bond of TBHP at elevated temperatures. Generation of acyl radicals in a similar manner are well documented for cyclization reactions involving heteroarenes and benzenoids.[153] Acyl radical **B** undergoes intramolecular ring closure to give fluorenone **1** after abstraction of a hydrogen radical from cyclohexadienyl radical **C**. As no concrete evidence for the direct involvement of water in the mechanism could be gathered and bearing in mind that the reaction does occur in water-free TBHP, albeit less efficiently, water was excluded from the proposed mechanism.



Scheme 26: Tentative mechanism of the TBHP-mediated oxidative cyclization of amines **173** and **184** to fluorenone (**1**).

TBHP-mediated cyclizations of similar nature have been previously reported in the literature, most commonly in combination with catalytic amounts of TBAI and sometimes accompanied by proposed mechanisms of their own.[133] Unfortunately, addition of TBAI for the cyclization of amine **184** did not increase the yield of fluorenone (**1**), on the contrary, it seemed to promote the generation of side products, judging by TLC-analysis. Based on these results, TBAI and other additives were generally not used in further experiments.

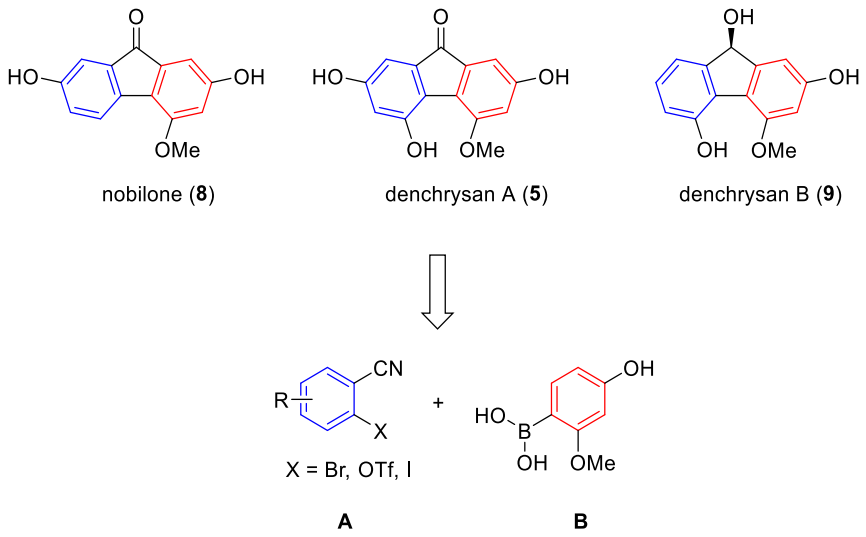
4 Synthesis

4.1 Synthesis of fluorenones

4.1.1 Total synthesis of the fluorenone-type natural product nobilone

4.1.1.1 Attempt at the total synthesis of nobilone with Bn-protected phenolic hydroxyl groups

Having successfully applied the TBHP-mediated cyclization for the synthesis of five fluorenones **1** and **1a-d**, the methodology was to be utilized for the synthesis of three fluorenone natural products, none of which had been previously synthesized: nobilone (**8**), denchrysan A (**5**) and denchrysan B (**9**). These three compounds were chosen primarily out of synthetic convenience, as they share the same substitution pattern on one of their benzene rings (highlighted in red in Scheme 27). Retrosynthetic analysis gives simple synthons **A** and **B** of similar structure as employed in the synthesis route for fluorenone.

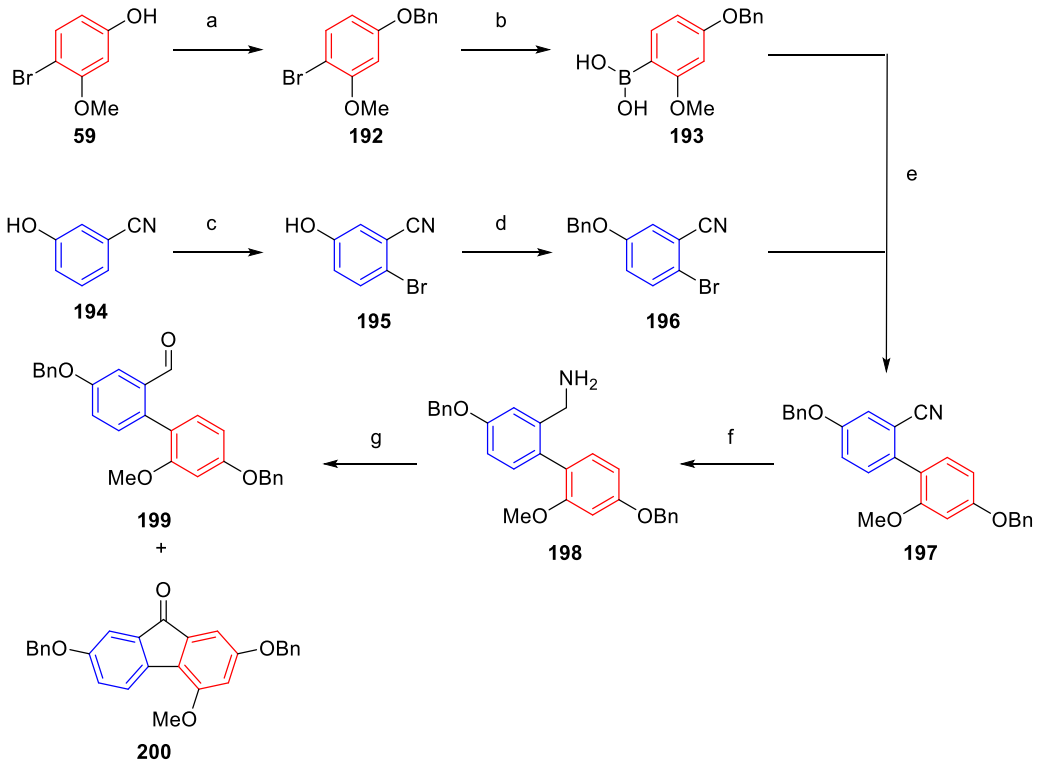


Scheme 27: Retrosynthetic analysis of fluorenone alkaloids.

However, a couple of additional aspects had to be taken into consideration. Firstly, primary amines were chosen as substrates for the TBHP-mediated cyclization instead of secondary *N*-methylamines, as starting materials leading to these precursors were more readily available from the corresponding nitriles. Secondly, the phenolic hydroxy groups common to the three target compounds were suspected to inhibit the TBHP-mediated radical cyclization. Typical phenolic radical inhibitors or antioxidants include compounds such as butylated hydroxytoluene (BHT) or vitamin E that generate resonance stabilized phenoxy radicals by scavenging highly reactive free radicals. The high polarity of alkaloid precursors with free hydroxyl groups might have also caused solubility problems during synthesis and reaction work-up. As such, phenolic hydroxy groups were protected as benzyl ethers, conventionally

employed for “permanent” protection, and removed during late stages of the synthesis, owing to their general robustness towards a wide range of reaction conditions.

For the synthesis of the boronic acid building block, commercially available 4-bromo-3-methoxyphenol (**59**) was *O*-benzylated by conventional means, and subsequently converted to boronic acid **193** (Scheme 28). For the benzonitrile building block, commercially available 3-hydroxybenzonitrile (**194**) was regioselectively brominated with *N*-bromosuccinimide (NBS) to give benzonitrile **195** as detailed by Wang and coworkers[154], followed by *O*-benzylation to afford the protected building block **196**. Both building blocks were then cross-coupled to afford Suzuki product **197** in high yield. For the reduction of 2-cyanobiphenyl **197**, lithium aluminium hydride (LAH) was employed as the reducing agent in addition to $AlCl_3$ which was shown to enhance LAH’s reduction potential in some cases[155], and primary amine **198** was furnished in a good yield. While generally not a necessity for nitrile reductions to proceed efficiently, some of the nitriles employed during synthesis of fluorenone precursors reacted rather sluggishly with LAH alone, prompting usage of a reaction enhancing additive. $AlCl_3$-induced cleavage of methyl ethers was not observed for any of the reactions performed.

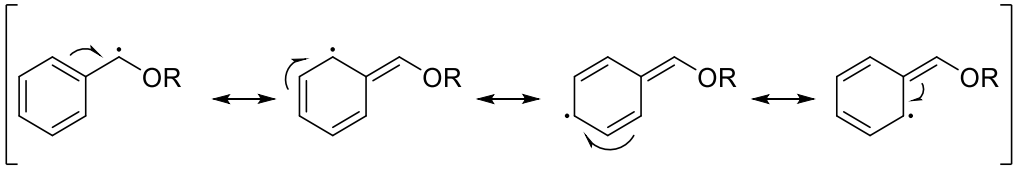


Scheme 28: Attempt at the total synthesis of nobilone (**8**). Conditions: a) K_2CO_3, BnBr, acetone, rt, 6 h, 92%; b) *n*-BuLi, $B(O^iPr)_3$, THF, -78 °C ⟶ rt, 16 h, 59%; c) $BF_3{\cdot}OEt_2$, NBS, MeCN, -20 °C ⟶ rt, 24 h, 51%; d) K_2CO_3, BnBr, DMF, 80 °C, 12 h, 61%; e) $Pd(PPh_3)_4$, Na_2CO_3, 1,2-DCE/H_2O (1:1), 100 °C, 12 h, 85%; f) LAH, $AlCl_3$, THF, 0 °C ⟶ rt,, 12 h, 71%; g) $TBHP_{aq}$, 1,2-DCE, 100 °C, 18 h, 37% (combined yield for product mixture).

Finally, amine **198** was reacted with TBHP to give a mixture of aldehyde **199** and the desired ketone **200**. While aldehydes are a common side-product of the TBHP-mediated cyclizations, the ratio was usually observed to be more heavily leaning towards the ketone. In this case,

however, the opposite seemed to have occurred, with the amount of aldehyde **199** furnished outweighing the amount of ketone **200** in an approximate ratio of 3:1 and the effective yield of ketone **200** being around 9%, as determined by ^{1}H NMR. Furthermore, purification *via* column chromatography proved difficult as both compounds had very similar R_f-values, complicating the isolation of either compound. With only small amount of impure compound left, the synthesis was discontinued at this point.

This unexpectedly poor result prompted a reexamination of the synthetic strategy. It was surmised that benzyl ether protecting groups may not adequately meet the demands of this route. Although generally chemically robust, benzyl ether protecting groups have been reported to undergo side reactions with free radicals[156], owing to benzyl radical stabilization (Scheme 28) and in this sense, may act as radical scavengers.



Scheme 29: Benzyl radical stabilization through delocalization.

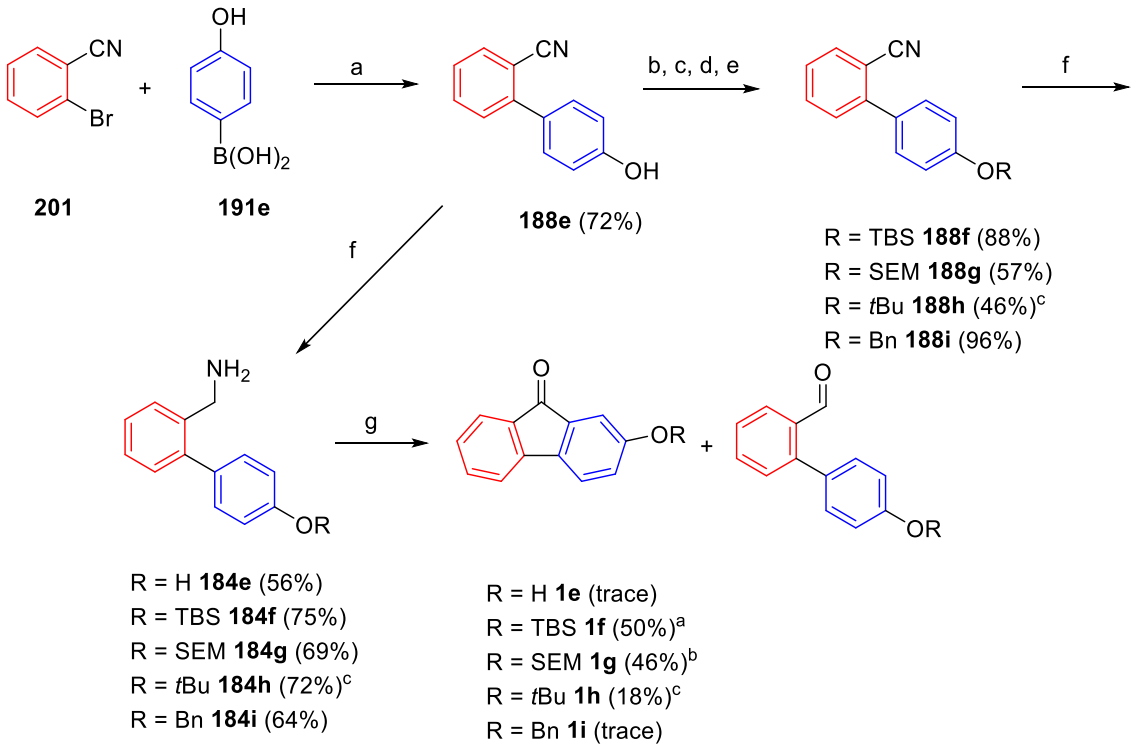
For this reason, it seemed plausible to assume the benzyl ether protecting group reacts with and therefore depletes the pool of free radicals available for cyclization to take place during reaction with TBHP, reducing the overall yield of the desired product while potentially leading to the generation of side-products. Although purely speculative, this might have also caused the skewed aldehyde to ketone ratio described previously, perhaps inhibiting the mechanism at a stage between amine oxidation and cyclization.

4.1.1.2 Model fluorenone synthesis for the determination of phenol protecting group compatibility towards the TBHP-mediated cyclization

In search of a more suitable protecting group, phenol protecting groups were tested for their compatibility towards TBHP-mediated cyclization with model fluorenones before further attempts at fluorenone natural product synthesis.

To satisfy the reaction conditions of the synthesis route, the ideal phenol protecting group had to be chemically inert against organolithium reagents at -78 °C (*n*-BuLi), alkaline conditions at elevated temperature (Suzuki conditions), strong reducing agents (LAH) in combination with Lewis acids ($AlCl_3$) and free radicals (generated by TBHP). Based on reaction condition compatibility charts in the literature[156], the *tert*-butyl protecting group appeared to be the most suitable protecting group in theory. Among the more commonly employed phenol protecting groups the *tert*-butyl(dimethyl)silyl (TBS) and the trimethylsilylethoxymethyl (SEM) groups were also deemed as suitable under the condition that they were to be introduced after Suzuki

coupling, as they are reportedly cleaved at elevated temperatures under strongly alkaline conditions.[157] The benzyl group was also added to the investigation to reaffirm its incompatibility with the TBHP-mediated cyclization with a model compound of simple structure. Following the established synthesis route, 2-cyanobiphenyl **188e** bearing a free phenol group was synthesized from 2-bromobenzonitrile (**201**) and boronic acid **191e** (Scheme 30).



Scheme 30: Synthesis of model fluorenones **1e-1i** in search of a suitable phenol protecting group. a) $Pd(PPh_3)_4$, K_2CO_3, DMF, 100 °C, 18 h; b) R = TBS: TBSCl, imidazole, DMF, 40 °C, 10 h; c) R = SEM: SEMCl, DIPEA, THF, rt, 24 h; d) R = *t*Bu: $Mg(ClO_4)_2$, Boc_2O, DCM, 40 °C, 24 h; e) BnBr, K_2CO_3, THF, rt, 16 h, 96%; f) LAH, $AlCl_3$, THF, 0 °C ⟶ rt, 16 h; g) TBHP, 1,2-DCE, 100 °C, 18 h; [a]approximated combinatory yield of pure, isolated product **1f** and a product mixture of ketone **1f** and aldehyde collected during purification by flash column chromatography; [b]approximated yield for a product mixture of **1g** containing ~16% aldehyde impurity; [c]crude yield for product mixtures of **188h**, **184h** and **1h** containing an unspecifiable amount of multiple impurities. The yield for product mixtures was approximated by ^1H NMR (for more information see Section 6.3).

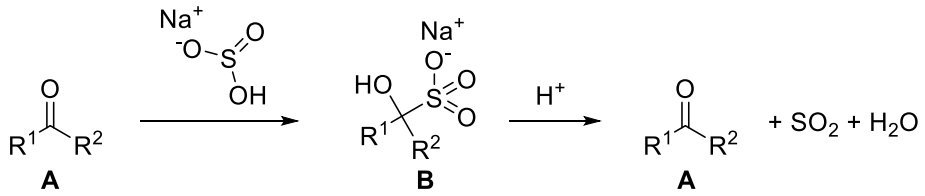
Protection of the phenolic hydroxy group already revealed significant differences. Silylation with TBSCl to give TBS-protected silyl ether **188f** proceeded smoothly with a yield of 88%, as did benzylation towards benzyl ether **188i**. SEM protection of phenol **188e** with SEMCl leading to SEM ether **188g** saw a decrease in yield in comparison. The most conventional method for the introduction of a *t*Bu-protecting group employs gaseous isobutylene under Lewis acid catalysis.[156] In lack of a (relatively expensive) isobutylene gas cylinder, the protecting group was introduced following a method described by Bartoli et al. with $Mg(ClO_4)_2$ and Boc_2O, also offering the advantage of ease of handling.[158] Unfortunately, this method of protection only led to a mediocre yield of 46% for compound **188h** next to multiple unidentified side-products. The protected compounds were then reduced with LAH and $AlCl_3$ with good yields ranging

from 64% to 75% to give the primary amines. The amine **184e** featuring an unprotected phenolic hydroxy group was also prepared with this method.

First, the amine **184e** bearing an unprotected phenolic hydroxy group was reacted with TBHP. The desired product 2-hydroxyfluorenone (**1e**) was only detected in trace amounts, demonstrating the necessity of a phenol protecting group for this reaction to proceed smoothly. Bn protection proved unsuitable as formation of fluorenone **1i** was also only detected in trace amounts and thus gave even worse results than for cyclization towards fluorenone **200**, likely for previously discussed reasons (Section 4.1.1, Scheme 29). Looking at the remaining (approximate) cyclization yields, it became clear that the *t*Bu-protecting group assumed to not negatively affect TBHP-mediated cyclization gave unexpectedly poor results with only about 18% conversion to fluorenone. The *t*Bu group should not be susceptible to side reactions with free radicals. In fact, the synthesis of a fluorenone bearing a *t*Bu group *via* a similar TBHP-mediated radical cyclization protocol has been previously reported to proceed in high yield.[159] However, the ^{1}H NMR spectra for the precursors **188h**, **184h**, as well as **1h** itself show non-negligible amounts of impurities that proved difficult to separate from either compound, the presence of which most likely negatively affected the cyclization yield. Nevertheless, the *t*Bu protecting group was ruled out as a potential candidate at this point because introduction also seemed inefficient with the method described previously. Meanwhile, the SEM protecting group achieved overall similar but slightly worse results than the TBS group, both during introduction thereof (88% for **188f** and 57% for **188g**, respectively) and yield of TBHP-mediated cyclization (50% for **1f** and 46% for **1g**, respectively). SEMCl is also far more expensive than TBSCl. Taking into consideration all contributing factors, the TBS group was ultimately chosen over the SEM group. Another rather common protecting group that seemed to satisfy the conditions set by the synthesis route in theory, cyclohexyl, was forgone as the TBS group ultimately gave satisfying results.

During TBHP-mediated cyclization of the amines, the issue of aldehyde-ketone mixtures arose again, as previously described for the attempt at the synthesis of nobilone (**8**). While a majority of the respective ketone was separable from the aldehyde in case of TBS, for *t*Bu- and SEM-protected amine cyclizations, the desired compounds eluted as compound mixtures even using disproportionally large chromatography columns and large amounts of silica gel during successive attempts at purification.

In an endeavor to completely separate the ketone-aldehyde mixture, the respective compound mixtures were subjected to a bisulfite-wash work-up.[160] The bisulfite-reaction is used to separate carbonyl compounds **A** from a compound mixture by forming water soluble bisulfite-adducts **B** with the carbonyl compounds (Scheme 31).



Scheme 31: The bisulfite reaction.

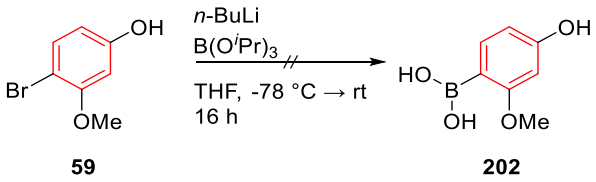
After separating the aqueous from the organic phase, the reaction can be reversed under acidic work-up conditions, setting the original carbonyl compound **A** free. In theory, the aldehyde should, compared to the fluorenone, be the preferred electrophile for the bisulfite to attack, owing to its lower steric hindrance and therefore higher reactivity towards nucleophilic addition. Unfortunately, and perhaps to be expected, the compound mixtures remained mixtures even after bisulfite work-up. While the ratio of ketone to aldehyde shifted towards the ketone by a negligible amount, judging by ^{1}H NMR spectrum, most of the compound mixture, including the ketone, reacted with bisulfite. In light of this issue, the yields given are approximated by addition of the yield of isolated pure ketone and estimated amount of ketone present in the residual aldehyde-ketone mixture. Alternatively, perhaps the aldehyde-ketone mixture could have been reacted with an oxidizing agent, which would ideally convert the aldehyde to the carboxylic acid and facilitate its separation from the unreacted ketone. This method was, however, not attempted at this point.

With no definite solution in hand, it was surmised that this issue was mostly aggravated by the bulky protecting groups and that the difference of the respective R_f-values of the aldehyde and ketone would increase upon deprotection, facilitating isolation *via* flash column chromatography (FCC). Without putting this theory to the test with the protected model fluorenones, the total synthesis of nobilone (**8**) was reattempted with the protecting group that gave the most promising results, the TBS group.

4.1.1.3 Total synthesis of nobilone with TBS protected phenolic hydroxy groups

First, the boronic acid building block **202** was to be synthesized *via* conversion of commercially available 4-bromo-3-methoxyphenol (**59**) with *n*-BuLi and B(O^{i}Pr)$_3$ as described by Konakahara et al. for 2-bromophenol (Scheme 32).[161] However, multiple attempts under these reaction conditions did not yield satisfactory results. Employing too little *n*-BuLi could constitute a conceivable mistake as the hydroxy group is deprotonated by *n*-BuLi during this reaction. An additional equivalent of *n*-Buli was added to account for this side reaction on an successive attempt. The reaction mixture gave an intense baseline spot during TLC-analysis in various elution systems, and it was surmised that the high polarity of the compound impeded extraction from the aqueous phase during work-up. No synthesis for boronic acid **202** has been reported in the literature to date, although it has been used as a starting material.[162] Preparation of

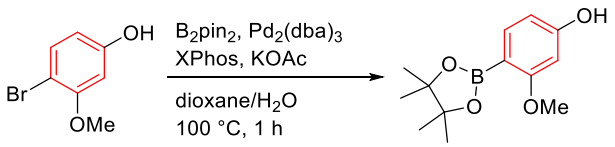
boronic acids of similar structure, such as 4-hydroxyphenylboronic acid[163], have been reported. In case the reaction was successful, extraction of the compound from the aqueous phase should therefore be possible at a sufficiently low pH level of about pH = 2. Nevertheless, with no apparent results, a different approach was taken.



59 **202**

Scheme 32: Attempt at the synthesis of boronic acid **202**.

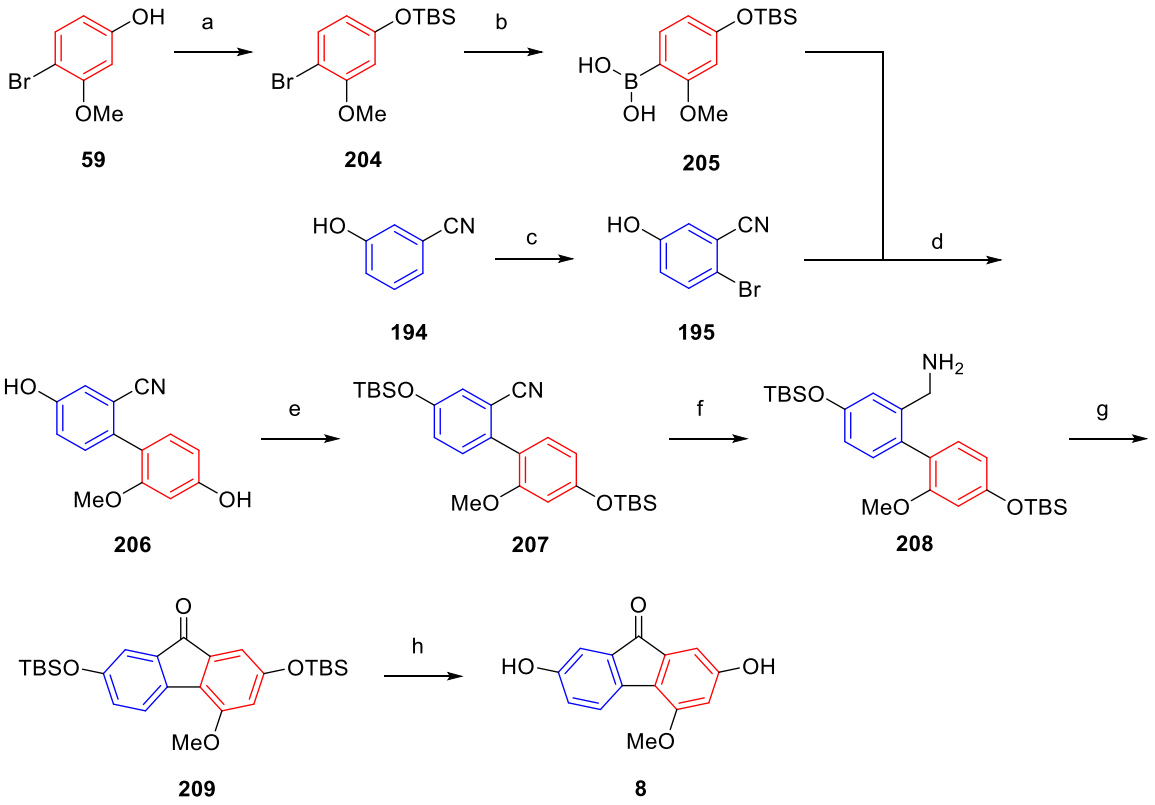
Next, synthesis of the pinacol boronic acid **203** was endeavored *via* Miyaura borylation (Scheme 33).[164] The best attempt yielded a product mixture as removal of residual B_2pin_2 proved challenging. While the reaction did work as determined by TLC-MS, unfortunately, the (crude) yield also turned out quite low and thus another option was taken into consideration.



59 **203** (32% crude yield, product mixture)

Scheme 33: Synthesis of pinacol boronic acid **203**.

As referenced earlier, the TBS protecting group is cleaved under Suzuki conditions. As such, introduction thereof was to be conducted after the two aryl moieties had been coupled. Considering the complications described for the synthesis of the boronic acid building block **202**, the phenolic hydroxy group was to be protected at this stage to decrease the polarity of the starting material and prevent side reactions with the free phenolic hydroxy group under the caveat that the TBS protecting group would most likely be cleaved during Suzuki coupling and would have to be reapplied afterwards. This synthetic strategy would add an additional step to the synthesis, but overall yield decrease was expected to be minimal as TBS protection often proceeds smoothly with close to quantitative yields. Ultimately, this method was chosen over employment of the pinacol boronic acid **203**, taking the higher projected overall yield into consideration.

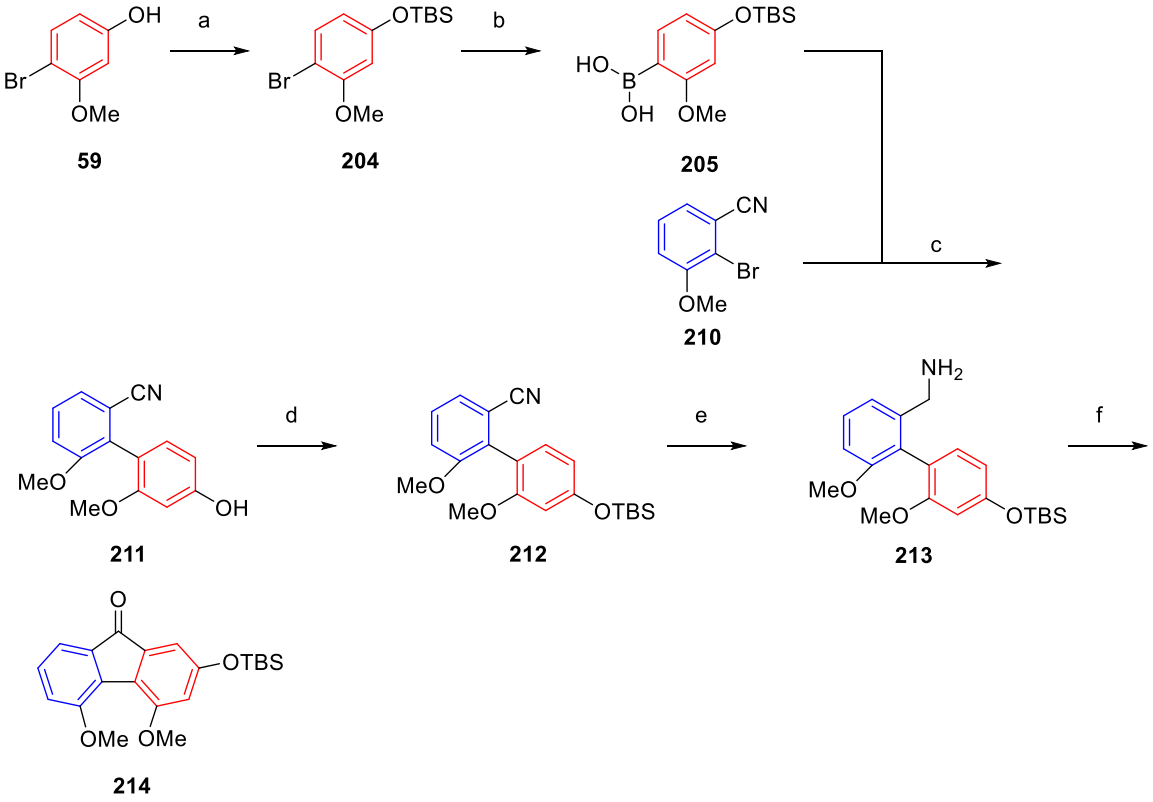


Scheme 34: Total synthesis of nobilone (**8**) with TBS protecting groups. Conditions: a) TBSCl, imidazole, DMF, 50 °C, 18 h, 97%; b) *n*-BuLi, $B(O^iPr)_3$, THF, -78 °C ⟶ rt, 16 h, 66%; c) $BF_3{\cdot}OEt_2$, NBS, MeCN, -20 °C ⟶ rt, 24 h, 51%; d) $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O (1:1), 100 °C, 12 h, 41%; e) TBSCl, imidazole, DMF, 50 °C, 18 h, 87%; f) LAH, $AlCl_3$, THF, 0 °C ⟶ rt,, 12 h, 80%; g) $TBHP_{aq}$, 1,2-DCE, 100 °C, 18 h; h) hydrogen fluoride pyridine, methoxytrimethylsilane, EtOAc, rt, 4.5 h, 58% over two steps. Total yield: 5% over 8 steps.

Following TBS protection of starting material **59**, the bromide **204** was reacted under the same conditions as previously described and gave boronic acid **205** in an acceptable yield of 66% (Scheme 34). The unprotected bromide building block **195**, which had already been synthesized during the previous attempt at the total synthesis of nobilone (**8**), was then coupled with boronic acid building block **205** under Suzuki conditions to give compound **206** in a, for this type of reaction, somewhat low yield of 41%. As expected, the TBS protecting group attached to the phenolic hydroxy group of boronic acid building block **205** was cleaved. The two phenolic hydroxy groups were then TBS-protected to give compound **207** prior to nitrile reduction with LAH and $AlCl_3$ to furnish primary amine **208** in a high yield of 80%. No $AlCl_3$-induced ether cleavage was observed. Next, the primary amine was cyclized with aqueous TBHP. As expected, this reaction gave an inseparable mixture of the desired product, ketone **209** and the aldehyde as the major side product. The crude product was deprotected using hydrogen fluoride pyridine complex, also referred to as Olah's reagent. Unfortunately, the R_f-values of the unprotected ketone and aldehyde still proved too similar to allow for a complete separation, and the natural product nobilone (**8**) was ultimately received with a yield of 58% over two steps and a purity of about 90%. The longest linear sequences was seven steps with an overall yield of 5% in a total of eight steps.

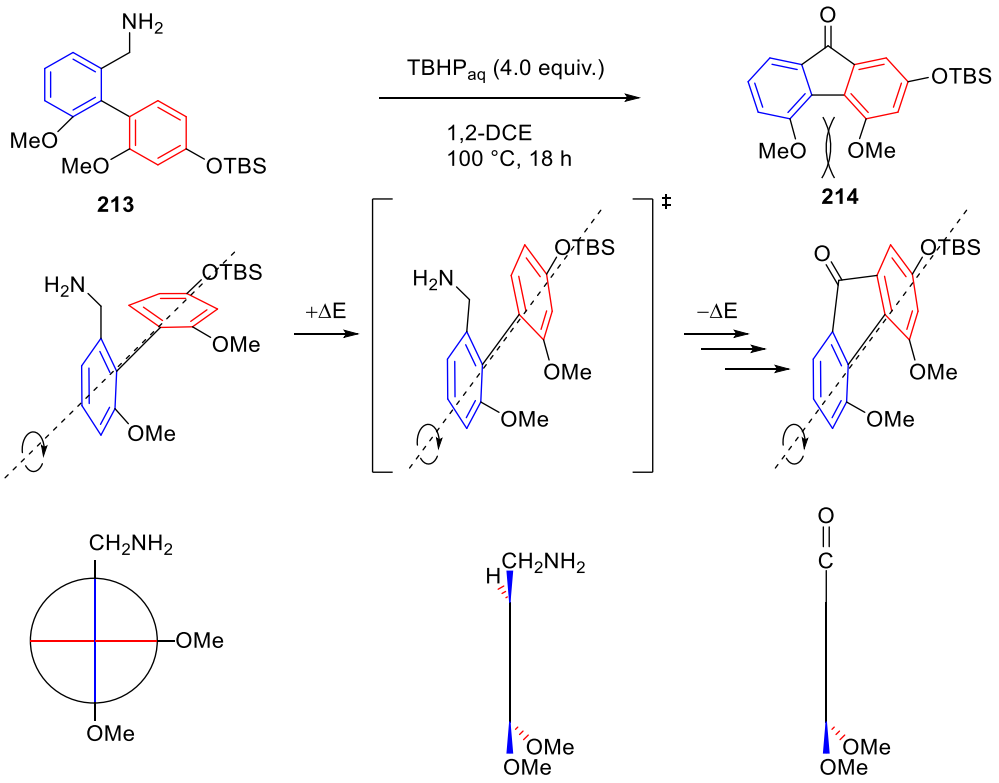
4.1.2 Further attempts at the total synthesis of fluorenone-type natural products

The synthesis of compound **214** followed the same general synthesis route starting from commercially available 2-bromo-3-methoxybenzonitrile (**210**), which was coupled with previously synthesized boronic acid building block **205** to give the deprotected Suzuki product **211** with a yield of 71% (Scheme 35).



Scheme 35: Total synthesis of compound **214**. Conditions: a) TBSCl, imidazole, DMF, 50 °C, 18 h, 97%; b) *n*-BuLi, $B(O^iPr)_3$, THF, -78 °C ⟶ rt, 16 h, 66%; c) $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O (1:1), 100 °C, 12 h, 71%; d) TBSCl, imidazole, DMF, 50 °C, 18 h, 88%; e) LAH, $AlCl_3$, THF, 0 °C ⟶ rt, 12 h, 90%; f) $TBHP_{aq}$, 1,2-DCE, 100 °C, 18 h, 4%.

After reapplication of the TBS protecting group, nitrile reduction gave amine **213** in a high yield of 90%. However, subsequent TBHP-mediated cyclization gave the fluorenone product **214** in a very low yield of 4%, presumably for steric reasons. Although no structure analysis has been conducted to support the following claims, one could imagine the two phenyl rings of amine **213** being twisted against one another in a pseudo-ecliptic conformation that allows the methoxy group of the phenyl ring to maintain spacial distance to the benzylamine ring's residues in *ortho*-position (Scheme 36). For cyclization to occur, one of the phenyl rings has to be rotated along the phenyl-benzylamine bond to arrange the molecule into a planar conformation. Forcing the mutually repelling residues into close vicinity in this manner requires more energy than if they were not present, and therefore the reaction might go poorly.



Scheme 36: Possible explanation for the poor cyclization yield of amine **213** towards fluorenone **214** through molecule conformations.

Originally, denchrysan B (**9**) was to be synthesized following the approach to nobilone (**8**). However, due to a transcription error, the wrong structure **215** was targeted. The correct structure of denchrysan B (**9**) is shown in Figure 4. The synthesis was discontinued at this point, but it was decided to discuss this synthesis nonetheless, as it gave further insight into potential limitations of the TBHP-mediated cyclization, in this case the steric hinderance of neighboring residues. Although the authors employed a different method, it should be noted that cyclization towards fluorenone with even bulkier neighboring residues in the same positions has been accomplished without apparent issues, contradicting the hypothesis detailed earlier as shown for the synthesis of dengibsin (**2**) by Jones and Ciske (Section 1.1.2, Scheme 6).[69]

Figure 4: Structures of the erroneously transcribed target molecule **215** and of denchrysan B (**9**).

In order to synthesize denchrysan B (**9**), the precursor **210** would have needed to bear a TBS-protected phenolic hydroxy group instead of a methoxy group. The synthesis route would have most likely run into the same issue during TBHP-mediated cyclization and afforded very little

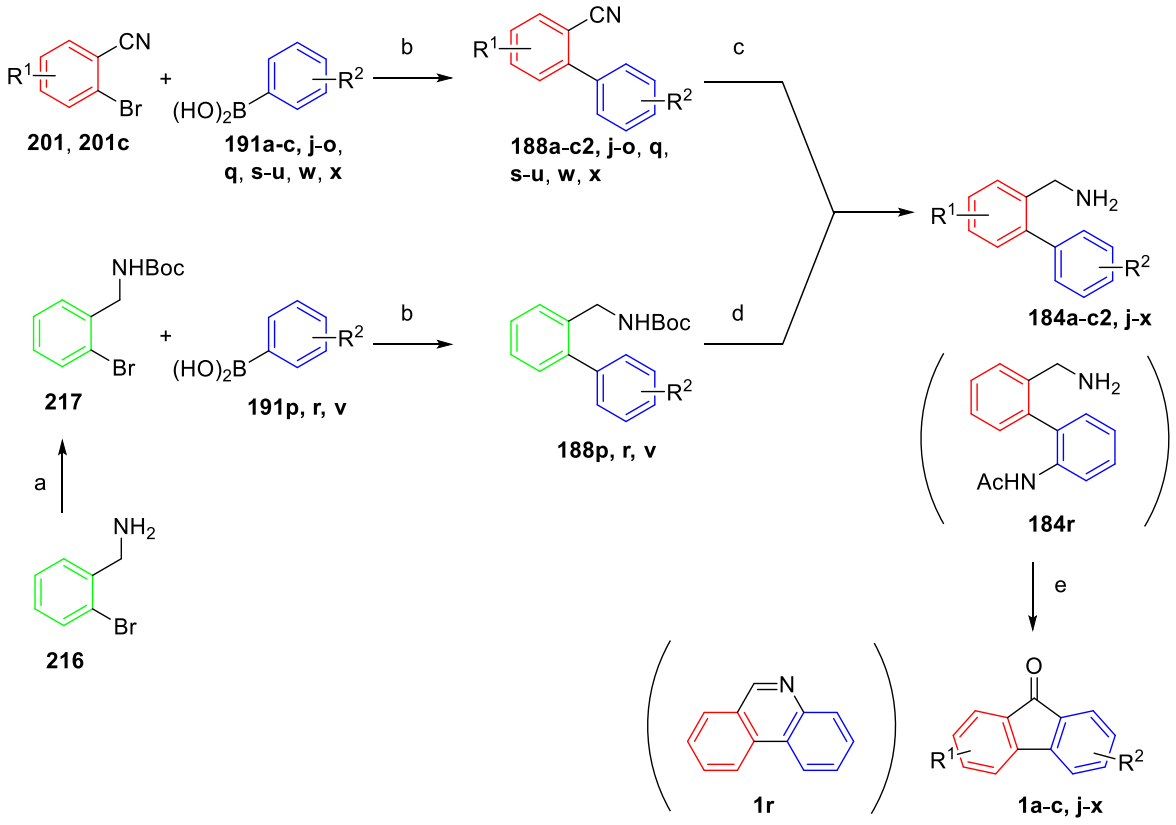
fluorenone, which then would have to be subjected to both a deprotection step and enantioselective ketone reduction to give denchrysan B (**9**).

In light of the poor cyclization yield of amine **213**, further attempts at the synthesis of both denchrysan B (**9**) and denchrysan A (**5**), bearing a similar C-4/C-5 substitution pattern, were abandoned.

4.1.3 Studies on the stereoelectronic effects of the TBHP-mediated cyclization

Aside from natural product synthesis, the scope and limitations of the TBHP-mediated cyclization of primary amines regarding substituent effects and compatibility were investigated.

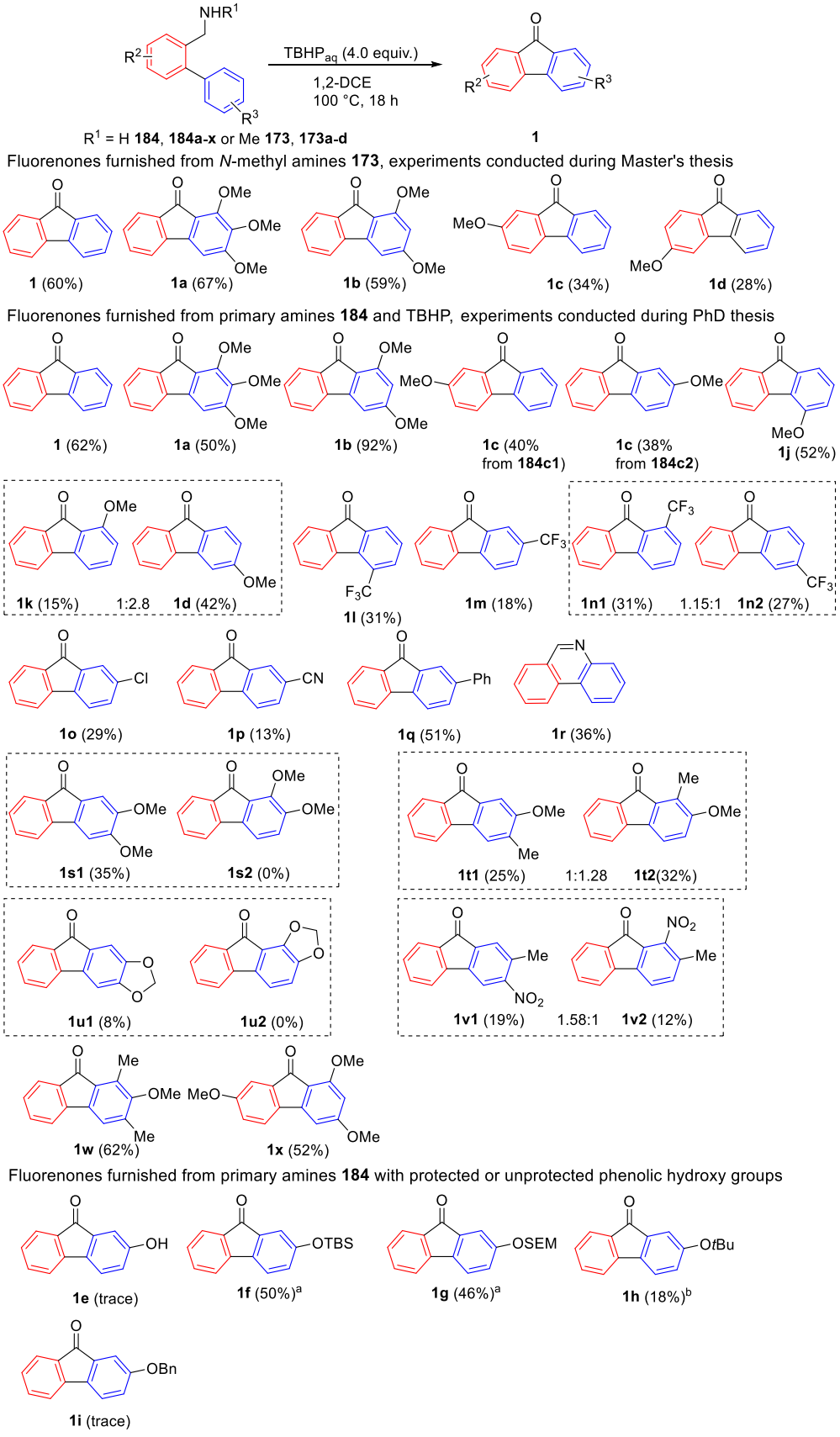
To this end, various substituted 2-(aminomethyl)biphenyls **184a-c2** and **184j-x** were converted to the corresponding fluorenones **1a-c** and **1j-x**. While the focus was on different methoxylation patterns, which naturally occurring fluorenones commonly bear, some electron withdrawing groups were also included in the investigation. The preparation of precursors bearing electron-withdrawing groups required a different synthetic approach than the one employed so far (Scheme 37).



Scheme 37: General synthetic routes for the synthesis of fluorenones **1**. Conditions: a) Boc_2O, NEt_3, DCM, rt, 18 h, 89%; b) $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O, 18 h, 100 °C, 70–99%; c) LAH, $AlCl_3$, THF, 0 °C ⟶ rt, 18 h, 39–92%; d) TFA, DCM, rt, 6 h, 76–98%; e) $TBHP_{aq}$, 1,2-DCE, 100 °C, 18 h, 0-92%.

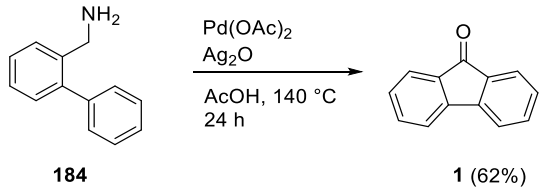
The established route furnished biphenyl-2-carbonitriles **188a-c2**, **j-o**, **q**, **s-u**, **w** and **x** with different substitution patterns, furnished from Suzuki coupling of commercially available 2-

bromobenzonitriles **201** and **201c** as well as phenylboronic acids **191**, **191a**-**c**, **j**-**o**, **q**, **s**-**u**, **w** and **x** in good yields ranging from 70–99%. The nitriles **188a**-**c2**, **j**-**o**, **q**, **s**-**u**, **w** and **x** were then reduced with LAH to give the primary amines **184 a**-**c2**, **j**-**o**, **q**, **s**-**u**, **w** and **x** in yields from 39–92%. Electron-withdrawing functional groups containing sp or sp^2 hybridized centers such as nitriles, amides, or nitro groups, are susceptible to reduction with complex metal hydrides. Therefore, the primary amine functional group was to be introduced without relying on reducing agents and running risk of transforming the electron-withdrawing functional groups in the process. This could be accomplished by coupling the respective phenylboronic acids **191p**, **r** and **v** with commercially available 2-bromobenzylamine (**216**) instead of 2-bromonitrile (**201**). The Suzuki reaction tends to work best with aryl halogenides furnishing electron-withdrawing groups in *ortho* or *para* position to increase their reactivity during oxidative addition of the reaction cycle.[165] Therefore, the electron-donating benzylamine group was converted into an electron-withdrawing *tert*-butyloxycarbonyl (Boc)-protected amino group prior to Suzuki coupling, which then had to be removed again before TBHP-mediated cyclization. Boc-protection of 2-bromobenzylamine (**216**) with Boc_2O and NEt_3 proceeded smoothly with a yield of 89% to give amide **217**. Subsequent reaction with the respective phenylboronic acids **191p**, **r** and **v** furnished the Suzuki products **188p**, **188r** and **188v**. The yield of the deprotection reactions to give primary amines **184p**, **184r** and **184v** with TFA ranged from 76-98% yield. This method adds an extra step in comparison to the nitrile route and was therefore only employed for substrates with substituents susceptible to reduction. The results of all performed TBHP-mediated cyclizations are shown in Scheme 38. As the four fluorenones **1a**, **1b**, **1c** and **1d** derived from the respective *N*-methyl-2-(aminomethyl)biphenyls **173a**, **173b**, **173c** and **173d** that were synthesized as part of my Master's thesis (Section 3, Scheme 24) and the fluorenones **1e**, **1f**, **1g**, **1h** and **1i** described earlier for the determination of a suitable protecting group (Section 4.1.1, Scheme 30) are discussed with regards to their electronic effects, they are also displayed in Scheme 38 for clarity's sake.



Scheme 38: Substrate scope for the oxidative cyclization of 2-(aminomethyl)biphenyls (yields in parentheses). Fluorenones furnished from a single amine precursor are grouped together in a dashed rectangle. Previously discussed fluorenones are also included for clarity's sake during comparison of substituent effects; [a]approximated yield for product containing compound mixture determined by ^{1}H NMR; [b]crude yield (for more information see Section 4.11, Scheme 30 and Section 6.3).

Of course, many of these fluorenones are or should be just as accessible from aldehydes and it may appear counterintuitive to convert aldehydes and nitriles to the corresponding amines first. However, with the exception of a single example[166] (Scheme 39), no studies on oxidative cyclizations of 2-phenylbenzylamines of this nature had been published in the literature up to this point, which prompted an in-depth exploration of this topic.



184 **1** (62%)

Scheme 39: Pd-catalyzed reaction of amine **184** to give fluorenone (**1**) reported by the Satyanarayana group.[166]

Presenting benzylamines as viable alternatives for TBHP-mediated cyclization precursors helps to broaden the synthetic prospects towards natural products bearing fluorenone cores. A variety of factors, such as the accessibility of starting materials, or the difference in reactivity or susceptibility of the respective synthesis intermediates may also favor one precursor over the other.

First, fluorenones **1a**, **1b** and **1c** were synthesized from primary amines **184a**, **184b**, and **184c** bearing the same meythoxylation patterns as *N*-methylamines **173a**, **173b** and **173c** leading to the same products. For 1,2,3-trimethoxyfluorenone (**1a**), the secondary amine **173a** gave a somewhat higher yield than the primary amine **184a** (67% and 50%). For 1,3-dimethoxyfluorenone (**1b**), primary amine **184b** as the substrate had the edge over the secondary amine **173b** (92% and 59%, respectively). Meanwhile, 2-methoxyfluorenone (**1c**) was furnished in 3 separate ways: from *N*-methylamine **173c** with the methoxy residue on the benzylamine ring (34%), the primary amine **184c1** with the methoxy residue on the benzylamine ring (40%) and the primary amine **184c2** with the methoxy residue on the radical accepting ring (38%). The yields for all three of these substrates were quite similar and which ring the methoxy group was attached to didn't seem to affect the yield significantly. This comparison was not carried out for the last *N*-methylamine **173d** as the starting material leading to the corresponding amine was not readily available. While some of these data points seem conflicting, it is to be expected that both primary amines and *N*-methylamines lead to roughly the same yields, bearing in mind that the yield of unsubstituted fluorenone (**1**) from unsubsituted *N*-methyl-2-(aminomethyl)biphenyl **173** and 2-(aminomethyl)biphenyl **184** are very similar (60% and 62%). No experiments with secondary amines bearing residues other than a methyl group at the nitrogen have been performed. Results with more bulky residues may vary.

Furthermore, it is also interesting to note, that TBS **1f** (50%) and SEM **1g** (46%) protected, and Ph-substituted **1q** (51%) variants were furnished in somewhat higher yields than the fluorenone **1c** furnished from the primary amine **184c2** with a methoxy residue in *para* position to the benzylamine ring (38%). The weakly ring-activating phenyl group gave the corresponding fluorenone in similar or higher yield than those amines with a strongly ring-activating alkoxy or silyloxy group. A clear correlation between the magnitude of ring activation and cyclization yield can not be established based on these data points. The primary amine **184j** with a methoxy residue in *ortho*-position to the benzylamine ring furnished the respective fluorenone **1j** is a somewhat higher yield of 52%. As expected, the meta-substituted amine **184k** gave a product mixture of the regioisomers 1- and 3-methoxyfluorenone (**1k**) and (**1d**) in a ratio of 1 to 2.8. The sterically less hindered 3-methoxy fluorenone (**1d**) was furnished in a yield of 42% and 1-methoxyfluorenone (**1k**) in a yield of 15% for a combined cyclization yield of 57%.

Next, a series of electron-withdrawing substituents were evaluated. Cyclization of the primary amine bearing a CF_3-substituent in *ortho*-position **184l** gave the corresponding fluorenone **1l** in a low yield of 31%. The *para*-substituted amine **184m** performed even worse with a yield of only 18% for fluorenone **1m**. In comparison to the respective derivatives of the methoxy-substituted series **1c** (from amine **184c2**) and **1j**, the yields decreased by about 20% each. Furthermore, *para*-substituted substrates seem to give the lowest yields in general. In comparison, the *meta*-substituted amine **184n** gave a relatively good, combined cyclization yield of 58% for **1n1** and **1n2**. Unlike the *meta*-substituted methoxy derivative **184k**, cyclization thereof seemed to exhibit little regioselectivity with a product ratio of 1:1.15 only slightly favoring sterically more hindered 1-(trifluoromethyl)fluorenone (**1n1**, 31%) over 3-(trifluoromethyl)fluorenone (**1n2**, 27%). This could perhaps be attributed to the relatively small size of the CF_3 moiety.

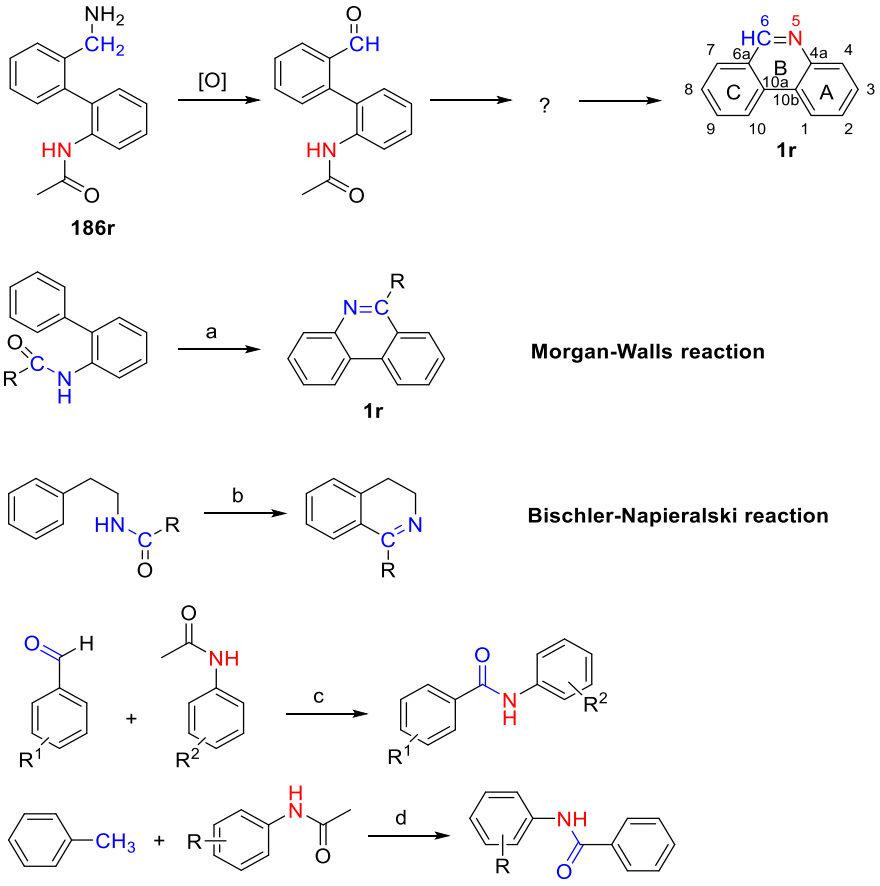
Comparing the yields of fluorenones **1m**, **1o** and **1p** derived from the *para*-substituted CF_3 (18%), chloro (29%) and nitrile (13%) derivatives, a clear trend is observable. The CF_3 group, exerting a strong -*I* effect, and the nitrile group, exerting a strong -*I* and -*M* effect, lower the yield to a greater degree than the chloro substituent, only exercising a weak -*I* effect, in comparison with *para*-substituents with electron donating effects. Electron-withdrawing groups in general seem to have an adverse effect on the cyclization yield (with the exception of *meta*-substituted amine **184n**), which is further pronounced by the magnitude of ring deactivation. These results could be rationalized on account of the electrophilic acyl radical reacting faster with electron-rich arenes, therefore facilitating cyclization, and slower with electron-deficient arenes.[167] However, the Studer group published a similar method for the synthesis of

fluorenones *via* TBHP-mediated cyclization of the corresponding aldehydes using catalytic amounts of $FeCp_2$ and found no such correlation.[159]

Surprisingly, the reaction of amine **184r**, bearing an acetamide residue in *ortho*-position, did not furnish any fluorenone but instead phenanthridine (**1r**) in a yield of 36%, forming a new 6-membered aromatic nitrogen-containing heterocycle.

Formation of similar 6-membered nitrogen-containing rings was not observed for any of the other starting materials. Bearing in mind mechanistic considerations made (Section 3.1), it is safe to assume that the nitrogen of the resulting phenanthridine (**1r**) originates from the amide group rather than the aminomethyl group (Scheme 40). Formal elimination of the aminomethyl group would require cleavage of a carbon-carbon bond, it is therefore more likely that the carbon atom of the new heterocycle originates from the aminomethyl group rather than the carbonyl group of the amide. This assumption is further backed by the absence of a methyl residue at C-6 of the cyclization product **1r**. The underlying mechanism is therefore decisively different in nature from reactions with similar starting materials and products like the Morgan-Walls synthesis of phenanthridine (**1r**), or the Bischler-Napieralski reaction that require oxophilic dehydration reagents (Scheme 40). For these reactions the carbon atom of the newly formed heterocycle stems from the amide functional group.

Oxidation of the aminomethyl group to the aldehyde has been observed in previous experiments. Therefore, the acyl radical is most likely a reactive intermediate. Meanwhile, experiments conducted during my Master's thesis also showed that TBHP-mediated cyclization of a secondary amide did yield the cyclization product fluorenone, albeit in a drastically lower yield (Section 3, Scheme 23). Based on these considerations, a possible reaction path towards phenanthridine (**1r**) could involve the intramolecular recombination of the acyl radical and the secondary amide radical. Radical-induced cleavage of the amide to give the amine and subsequent intramolecular imine condensation seems unlikely as there are a number of publications that report on the construction of amides using TBHP rather than their cleavage.[168] Copper(II)- and iodine-catalyzed methods for the TBHP-mediated intermolecular coupling of benzaldehydes and acetanilides to give benzanilides have been reported by Chen et al. and Kumar et al. (Scheme 40, reactions c and d), respectively, although neither report mentions the formation of the respective imines.[169] Assuming the intramolecular reaction observed for amine **184r** follows a similar pathway, albeit in absence of catalysts, it would have to proceed *via* a lactam intermediate. However, reduction thereof to phenanthridine (**1r**) should not be facilitated given the oxidizing reaction conditions. Ultimately, the mechanism for this unexpected reaction remains unclear.



Scheme 40: Considerations regarding the formation of phenanthridine (**1r**) from amine **184r**. Conditions: a) $POCl_3$, nitrobenzene, reflux; b) $POCl_3$, benzene, reflux; c) TBHP (2.0 equiv.), $CuCl_2 \cdot 2H_2O$, DCE, 100 °C, 24 h ; d) I_2 (1.0 equiv.), TBHP (3.0 equiv.), 80 °C, 24 h.

While no appropriate experiment was conducted, it is reasonable to assume that the reaction might succeed if the acetamide residue occupied a *meta*- or *para*-position on the phenyl ring as it would be less likely to react with the aminomethyl group, at least intramolecularly.

Next, a series of asymmetrically disubstituted amines **184s**, **184t**, **184u** and **184v** were reacted (Scheme 38). Amines **184s** and **184t** both bear a methoxy residue in *para*-position but differ in their substituent at the *meta*-postion, amine **184s** bearing a methoxy residue and amine **184t** a methyl residue. Surprisingly, cyclization of amine **184s** only gave the sterically less hindered regioisomer 2,3-dimethoxyfluorenone (**1s1**) in a yield of 35%. Amine **184t** furnished both expected regioisomers displaying little regioselectivity with yields of 25% for 2-methoxy-3-methylfluorenone (**1t1**), 32% for 2-methoxy-1-methylfluorenone (**1t2**) and a combined cyclization yield of 57%. Again, the small size of the methyl substituent may result in no significant steric hindrance. In this case, a methoxy residue in *meta*-position furnished the fluorenone in a higher yield than with a methyl substituent, although the total cyclization yield is considerably lower. No second stereoisomer for the cyclization of amine **184s** was found so a direct comparison with cyclization of amine **184t** lacks genuine informational value. Amine **184u** bearing a methylendioxy residue only gave the sterically less hindered isomer **1u1** in a very low yield of 8%. The methylendioxy carbon might act as a radical scavenger or undergoes

side reactions with free radicals, drastically reducing the yield in comparison to fluorenone **1s** furnished from structurally similar amine **184s**. Amine **184v** bearing a nitro group and a methyl group gave two regioisomers **1v1** and **1v2** in 19% and 12% yield, respectively. As observed with other examples, the effect of the strong electron-withdrawing nitro group lowered the combined cyclization yield (31%) in comparison to other asymmetrically substituted amines by about 20%, also overpowering the weak electron-donating effect of the methyl group.

Finally, two trisubstituted amines were cyclized with TBHP. Amine **184w** furnished 2-methoxy-1,3-dimethylfluorenone (**1w**) in a comparatively good yield of 62%, which places it between structurally similar 1,2,3-trimethoxyfluorenone (**1a**) furnished from the *N*-methylamine **173a** (67%) and the primary amine **184a** (50%) yieldwise. Meanwhile, 1,3,7-trimethoxyfluorenone (**1x**) was furnished in a yield of 52%. This yield is marginally or considerably lower than the yields for structurally similar 1,3-dimethoxyfluorenone (**1b**), furnished from either the *N*-methylamine **1b** (92%) and the primary amine **184b** (57%), respectively.

In summary, electronic effects were observed to affect the TBHP-mediated cyclization partially. Considering unsubstituted fluorenone (**1**) as the baseline, electron-donating groups either exerted a weakly positive or negative influence on the yield, depending on the substitution pattern, yielding fluorenones in the range of about 40-60%. Meanwhile, electron-withdrawing groups mostly reduced the yield compared to electron-donating groups in the same positions, the degree of which seemed to depend on the functional group's magnitude of ring deactivation. Amines with electron-withdrawing groups yielded fluorenones in the range of about 15-30%. There also seems to be a trend regarding substitution patterns, whereas the *para*-position gave comparatively less favorable results than the *ortho*-position. An amine with an acetamide residue in *ortho*-position gave phenanthridine (**1r**) instead of fluorenone. Amines with substituents prone to side-reaction with free radicals gave only trace amounts of the desired products. The TBS and SEM protecting groups for phenolic hydroxy groups proved to be compatible with the TBHP-mediated cyclization, while Bn- and *t*Bu-protected substrates gave very low or trace amounts of the desired product. However, the results for *t*Bu might be misleading due to the presence of impurities in the substrate **184h** (see Section 4.1.1.2, Scheme 30). Part of this research topic was published in the Beilstein Journal of Organic Chemistry.[170]

4.2 Side project: Attempts at the total synthesis of azafluoranthene-type alkaloids

Azafluoranthenes are a small class of polycyclic aromatic hydrocarbons (PAH) found in flowering plants of the *Menispermaceae* family. Structurally they are composed of a benzene and an isoquinoline moiety which are connected by a five-membered ring. Members of this

alkaloid class like norrufscine[171] (**218**) or norimeluteine[172] (**219**) both isolated from *Cissampelos pareira* have been found to exhibit cytotoxic and anti-HIV activity (Figure 5). Just like fluorenones and azafluorenones, fluoranthenes and azafluoranthenes have also attracted attention for their potential applications in material science, for example as fluorescent bioprobes[173] or organic dyes.[174]

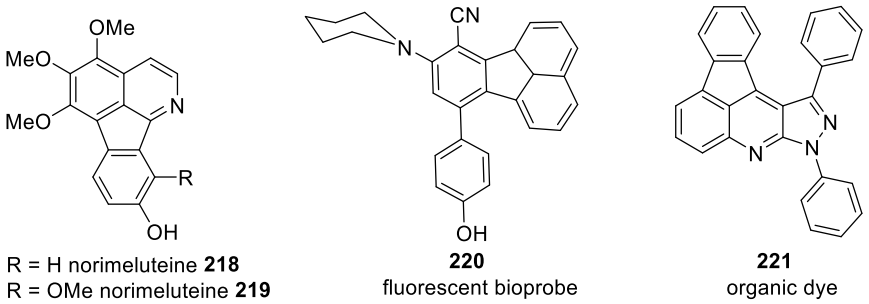
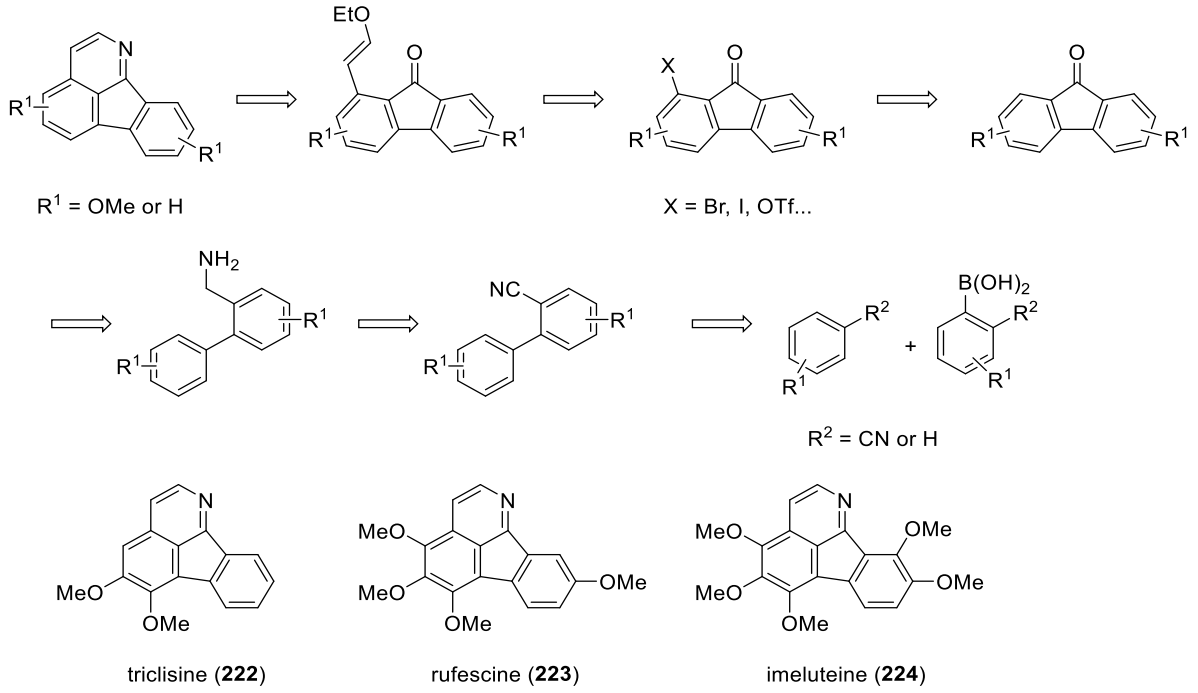


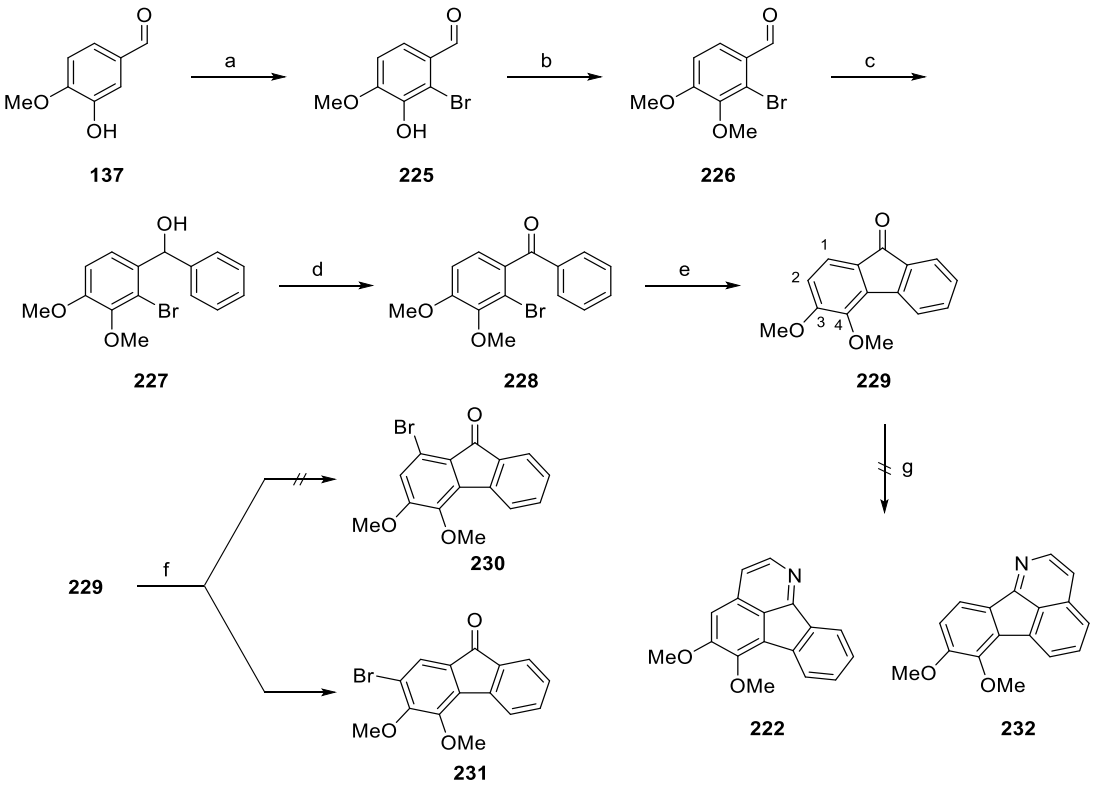
Figure 5: Selection of azafluoranthene alkaloids and noteworthy synthetic derivatives.

A general synthesis route for azafluoranthene alkaloids was roughly envisioned based on the newly developed synthesis route for fluorenones (Scheme 41). The final step represents a pyridine ring annulation *via* condensation of a masked 1,5-dicarbonyl moiety with ammonium acetate in glacial acetic acid. This chemistry allows for the synthesis of a variety of condensed heterocycles and has been previously utilized by the Bracher group for the preparation of analogues of the alkaloids sampangine (**81**) and cleistopholine (**84**)[175] as well as 1-substituted β-carbolines.[176] With most of the chemistry of the tentative synthesis route established, the only challenge in theory was the regioselective introduction of a halogenide substituent at C-1 of the fluorenone intermediate to allow subsequent cross-coupling with 2-ethoxyvinylboronic acid pinacol ester. The primary target alkaloids were triclisine (**222**), rufescine (**223**) and imeluteine (**224**), which only differ in the number and position of methoxy groups attached to the fluorenone synthon.



Scheme 41: Late-stage halogenation approach to the retrosynthesis of azafluoranthenes featuring 1-halofluorenones as a key intermediate and primary target compounds triclisine (**222**), rufescine (**223**) and imelueine (**224**).

It quickly became clear, however, that the synthesis route *via* TBHP-mediated cyclization required starting materials that were either too expensive or arduous for bulk preparation. This was especially disadvantageous considering a proof of concept for the synthesis route had not yet been established in practice, necessitating larger quantities of substrate to experiment with. Therefore, 3,4-dimethoxyfluorenone (**229**), as an intermediate towards the target alkaloid with the least demanding substitution pattern, triclisine (**222**), was prepared with slight modification made to the method described by Silveira and coworkers (Scheme 42).[177]

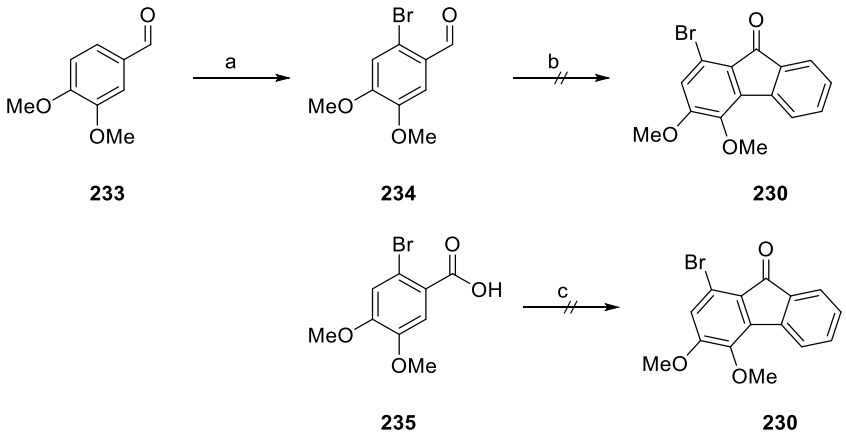


Scheme 42: Synthesis of 3,4-dimethoxyfluorenone (**229**) and attempted C-1 bromination. Conditions: a) NBS, DCM, rt, 30 min, 95%; b) K_2CO_3, MeI, DMF, rt, 16 h, 93%; c) Mg, BrPh, Et_2O, rt, 2 h, 63%; d) MnO_2, DCM, rt, 16 h, 87%; e) KOAc, K_2CO_3, $Pd(PPh_3)_4$, DavePhos, DMA, rt, 2 h, 68%; f) Br_2, HOAc, rt, 18 h, 9%; g) first aminoacetaldehyde-dimethyl acetal, toluene, 100 °C, 4 h, then TFAA, BF_3 $(AcOH)_2$, 18 h.

Regioselective bromination of commercially available isovanillin (**137**) with NBS[178] and subsequent *O*-methylation gave aldehyde **226**. The Grignard reagent PhBrMg was freshly prepared *in situ* from phenyl bromide and Mg in THF, to which a solution of aldehyde **226** was added dropwise to give the secondary alcohol **227** in 63% yield. Oxidation to the benzophenone **228** was accomplished with MnO_2 in high yield, rather than pyridinium dichromate like Silveira et al. had used. Finally, submission of **228** to $Pd(PPh_3)_4$-catalyzed cyclization in *N*,*N*-dimethylacetamide (DMA), with the phosphine ligand DavePhos and a base mixture of KOAc and K_2CO_3 furnished 3,4-dimethoxyfluorenone (**229**) in 68% yield. 3,4-Dimethoxyfluorenone (**229**) was then suspended in acetic acid followed by dropwise addition of Br_2. The reaction proceeded very slowly with most of the starting material not having been consumed after 18 h and gave the 2-bromo derivative **231** with a yield of 9%. Seeing that the wrong regioisomer had formed, it became evident that late-stage bromination of fluorenones would not lead to the desired product, and no attempts at reaction optimization were made. 3,4-Dimethoxyfluorenone (**229**) was also reacted under Pomeranz-Fritsch conditions in an attempt to circumvent the need for C-1 ethoxyvinylation altogether. To this end, the fluorenone **229** was to be converted to an imine with aminoacetaldehyde-dimethyl acetal and cyclized to the desired heterocycle triclisine (**222**), ideally in a favorable isomeric ratio. This chemistry has been previously employed by the Bracher group for the construction of a isoquinoline moiety

from a benzaldehyde subunit for the first total synthesis of the dimeric isoquinoline-isoquinolone alkaloids berbanine and berbidine.[179] Unfortunately, the starting material **229** barely reacted under these conditions and the product mass could not be identified from the crude reaction mixture. Surprisingly, it appeared that imine formation proceeded very slugglishly if at all.

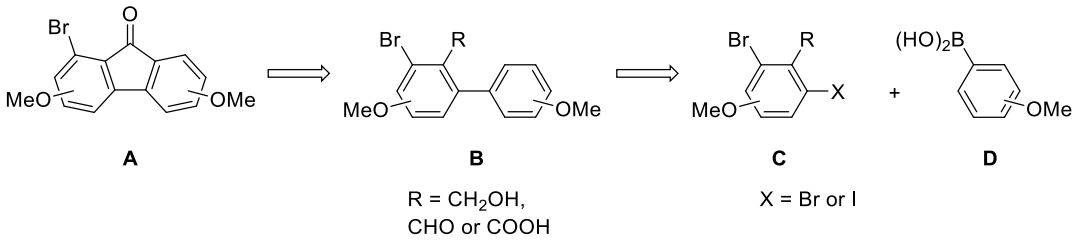
As late-stage bromination did not favor installation of a bromo substituent at C-1, the next attempts were made with the bromo substituent already situated at the correct ring-positions of the starting material. First, two one-pot protocols for the synthesis of fluorenones from aldehydes were attempted (Scheme 43). The Sorensen group published a method for the synthesis of fluorenenones from benzaldehydes and aryl iodides *via* Pd(II)-catalyzed C(sp^2)-H functionalization cascade with anthranilic acid, AgTFA in AcOH/hexafluoroisopropanol (HFIP).[180] The reaction scope reported included multiple examples of 1-halofluorenones. Another publication by Sun et al. reported on the one-pot cascade reaction consisting of *ortho*-selective cross-coupling between benzoic acids and arenes and subsequent intramolecular Friedel-Crafts-type acylation.[72] The method reportedly also allows for facile synthesis of 1-halofluorenones. After preparing or purchasing the appropriate starting materials **234** and **235**, however, neither of these methods furnished the desired product **230**. The product mass was not found in either crude reaction mixture, therefore these avenues were not further explored.



Scheme 43: Attempts at the synthesis of 1-bromo-3,4-dimethoxyfluorenone (**230**) with one-pot methods. Conditions: a) Br_2, MeOH 0 °C → rt, 3 h, 86%; b) iodobenzene, $Pd(OAc)_2$, anthranilic acid, AgTFA, AcOH/HFIP, 120 °C, 36 h; c) benzene, $Pd(OAc)_2$, Ac-Ile-OH, $Na_2S_2O_8$, DMSO, TfOH, 80 °C, 24 h.

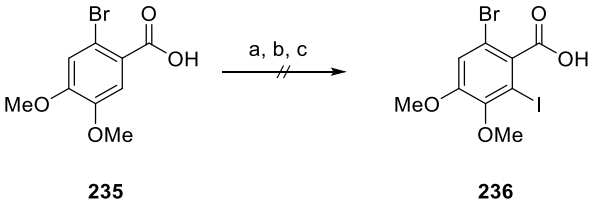
As one-pot protocols were not successful, the 1-bromofluorenone **A** was to be constructed successively starting from an appropriately dihalogenated precursor **C** (Scheme 44). For precursors with asymmetric substitution patterns, as in the case for the precursor for triclisine (**222**), the position to be first reacted by coupling with the phenylboronic acid precursor had to be iodinated. The difference in reactivity between bromide and iodide substituents towards Suzuki coupling should therefore give the desired coupling product. Suzuki coupling was envisioned to furnish either biphenyl-2-carboxaldehyde, biphenyl-2-carboxylic acid or the

biphenyl-2-methanol **B** from which ring closure *via* TBHP-mediated radical cyclization or intramolecular Friedel-Crafts acylation in strongly acidic media should give the 1-bromoazafluorenone **A**.



Scheme 44: Early-stage halogenation approach to the retrosynthesis of 1-bromofluorenone intermediates.

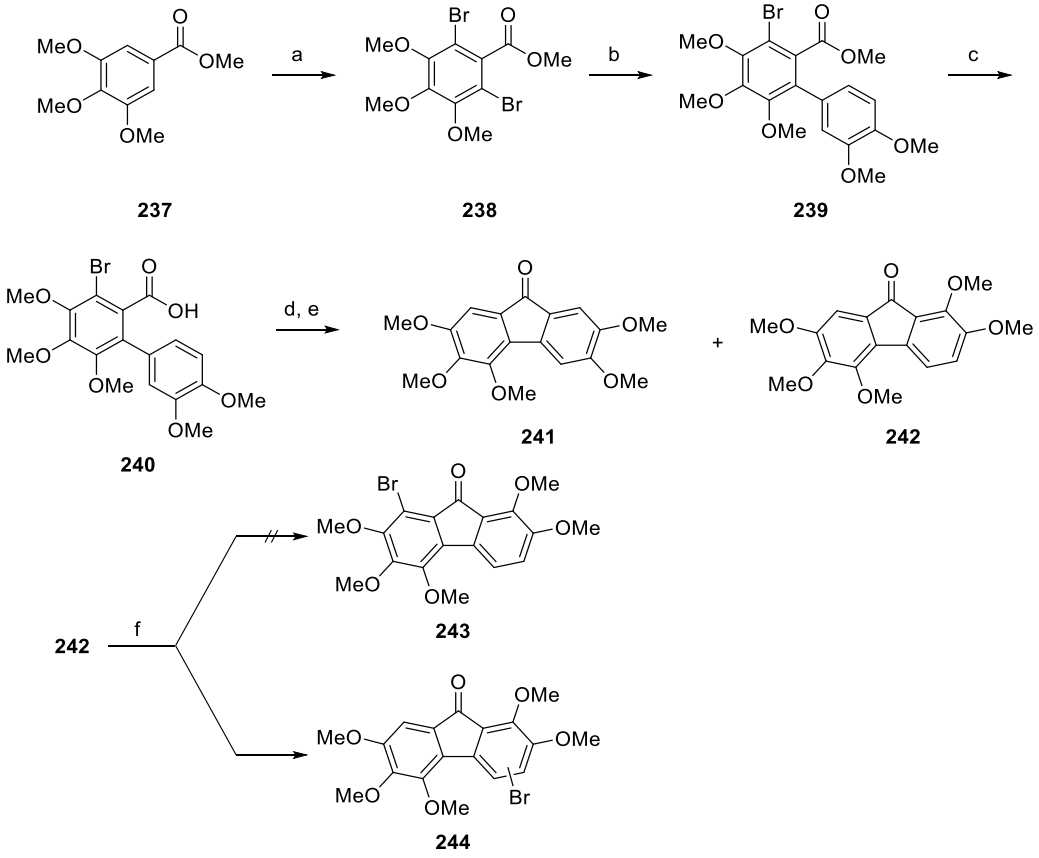
Preparation of the dihalogenated benzoic acid **236** proved unexpectedly challenging and has not been reported in the literature. Three different iodination protocols were attempted. Al-Zoubi et al. reported a method for the regioselective *ortho*-iodination of benzoic acids, where the substrate is reacted with $Pd(OAc)_2$, iodobenzene diacetate and iodine in anhydrous DMF under nitrogen atmosphere for 24 h. C-6 iodination of 2-bromobenzoic acid was also accomplished with this method.[181] Similar reaction conditions were also reported by the Zhao group for the synthesis of a 2-bromo-6-iodobenzoic acid precursor for the preparation of diaryl acetylene antiproliferative agents, although NIS was used as the iodine source.[182] Finally, Ruiz and coworkers used I_2 and CF_3CO_2Ag for the selective *ortho*-iodination of benzyl alcohols with different methoxy substitution patterns.[183] Unfortunately, none of these protocols furnished the desired product judging by TLC-MS analysis of the crude reaction mixtures. In fact, it appeared as if the majority of the starting material had not reacted following any of these procedures.



Scheme 45: Attempts at regioselective iodination of benzoic acid **235**. Conditions: a) $Pd(OAc)_2$, iodobenzene diacetate, iodine, DMF, 24 h, 100°C; b) $Pd(OAc)_2$, NIS, DMF, 100 °C, 12 h; c) I_2, CF_3CO_2Ag, DCM, rt, 30 mins.

At this point, attention was shifted towards the more readily accessible precursors for the alkaloids rufescine (**223**) and imeluteine (**224**). In contrast to the hypothetical precursor **236** for triclisine (**222**), there was no need to differentiate between the two positions *ortho* to the ester functional group of methyl 3,4,5-trimethoxybenzoate (**237**) due to its symmetrical methoxylation pattern. In case rufescine (**223**) and imeluteine (**224**) were prepared successfully, synthesis of triclisine (**222**) was to be revisited at a later point.

Dibromination of methyl 3,4,5-trimethoxybenzoate (**237**) gave the product **238** in 99% yield (Scheme 46). The Suzuki product **239** was obtained from reaction with 3,4-dimethoxyphenylboronic acid in 49% yield. Although 3,4-dimethoxyphenylboronic acid was not the cross-coupling partner of choice for the synthesis of imeluteine (**224**), it was chosen over the more suitable 2,3-dimethoxyphenylboronic acid as the latter was not available from chemical vendors at the time and 3,4-dimethoxyphenylboronic acid was thought to serve its purpose for establishing a proof of concept for the synthesis route. Oddly, the Suzuki reaction did not work with K_2CO_3 but employment of Cs_2CO_3 as the base instead gave the desired product **239**. To minimize formation of the dicoupling product, only 1.0 equivalents of the 3,4-dimethoxyphenylboronic acid was used instead of the usual 1.5 equivalents. As expected, the yield was somewhat lower compared to other Suzuki couplings performed.

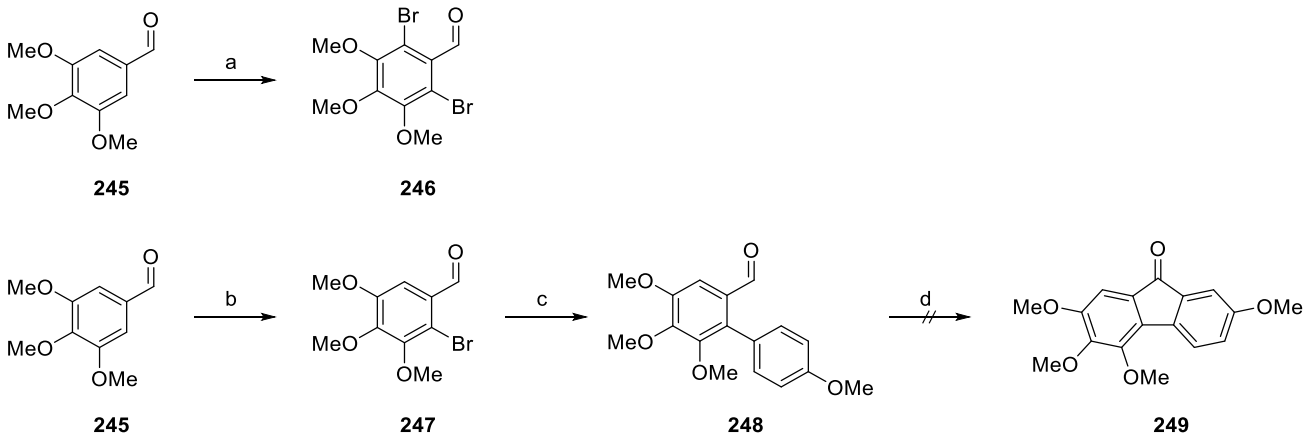


Scheme 46: Attempted synthesis of bromofluorenone **243**. Conditions: a) NBS, MeCN, 60 °C, 18 h, 99%; b) 3,4-dimethoxyphenylboronic acid, $Pd(PPh_3)_4$, $CsCO_3$, DMF/H_2O (1:1), 100 °C, 16 h, 49%; c) KOH, H_2O/EtOH, 100 °C, 16 h; d) PPA, 140 °C, 1 h; e) MeI, K_2CO_3, 16 h, rt, 44% **241** and 12% **242** over three steps; f) NBS, MeCN, 60 °C, 18 h, 8% (crude yield).

PPA-mediated cyclization of the ester **239** did not yield any fluorenone product. The ester **239** was thus subjected to alkaline ester hydrolysis to give the crude carboxylic acid **240** before renewed PPA-mediated cyclization. The reaction again did not give the desired product but instead a mixture of demethylated fluorenones, judging by mass spectrocopic analysis of the crude reaction mixture. The crude mixture was therefore reacted with K_2CO_3 and MeI and gave the two isomeric fluorenones **241** and **242**. As anticipated, the reaction had furnished a mixture

of isomers, favoring formation of the sterically less hindered isomer **241** in a yield of 44%, while the isomer of interest **242** was obtained with a low yield of only 12%. This issue could be circumvented by employing 2,3-dimethoxyphenylboronic acid as the cross-coupling partner for the Suzuki reaction rather than 3,4-dimethoxyphenylboronic acid, leaving only one site of attack during cyclization of the 2-biphenylcarboxylic acid which should therefore exclusively lead to the desired isomer. However, the bromide substituent had been inexplicably removed during the reaction. The cause is unclear as neither the conditions employed for the PPA-mediated cyclization, nor the methylation reaction should facilitate reductive debromination of aryl bromides. An attempt at reintroduction of the bromide substituent with NBS in MeCN failed, as bromination occurred at the wrong benzene ring, leading to one of two possible, undesired bromofluorenones **244**. The reaction itself proceeded slowly with most of the starting material not having been consumed after 16 h to give an impure compound in very low yield, which did not allow for a full analytic characterization thereof. As the desired product had not formed, no further attempts at reaction optimization were made.

Because intramolecular Friedel-Crafts-type cyclization in strongly acidic media had failed, TBHP-mediated radical cyclization was attempted (Scheme 47). To this end, commercially available 3,4,5-trimethoxybenzaldehyde (**245**) was reacted with 2.1 equivalents of NBS. Oddly, the reaction did not proceed as smoothly as dibromination of the corresponding ester **238** and gave a mixture of mono and dibrominated compound, along with several unidentified by-products. Notably, the reaction seemed to stop at the monobrominated aldehyde **247** with further bromination procceding very sluggishly even after increasing the reaction time and temperature as well as addition of more NBS. Unfortunately, both the mono- and dibrominated species had very similar R_f-values in most commonly employed eluent systems which made isolation of either compound *via* column chromatography arduous.



Scheme 47: Attempted synthesis of fluorenone **249**. Conditions: a) NBS (2.6 equiv.), MeCN, rt → 60 °C, 72 h; b) NBS, MeCN, 60 °C, 18 h, 80%; c) 4-methoxyphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF/H_2O (1:1), 100 °C, 16 h, 85%; d) $TBHP_{non}$, 1,2-DCE, 100 °C, 18 h.

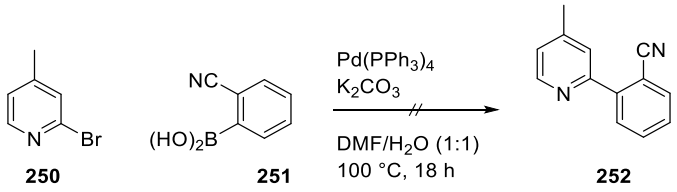
The reaction was set aside, and the route was continued with the monobrominated aldehyde **247** which was obtained from reaction of 3,4,5-trimethoxybenzaldehyde (**245**) with 1.1 equivalents NBS in 80% yield. The Suzuki coupling product **248** was obtained from reaction with 4-methoxyphenylboronic acid in 85% yield. Unlike for biphenyl ester **239**, employment of Cs_2CO_3 instead of the usual base K_2CO_3 was not necessary for the coupling reaction to work. The 2-biphenylcarbaldehyde **248** was then subjected to the standard conditions for TBHP-mediated cyclization. Unfortunately, under these conditions the starting material **248** barely reacted. While a few unidentified side-products appeared during TLC-analysis, the respective TLC spots were very low in intensitiy and did not match the product mass. TBHP-mediated cyclization of substrates bearing up to three methoxy substituents towards fluorenones has been accomplished previously as part of this thesis (Section 4.1.3, Scheme 39). This was the first attempt at cyclization of a substrate bearing four methoxy groups. Perhaps the high electron density of aldehyde **248** impedes TBHP-mediated cyclization thereof. With neither PPA-mediated cyclization nor TBHP-mediated cyclization furnishing the respective desired products, no further attempts at azafluoranthene synthesis were made.

Arguably, modifications to this synthesis route have not been explored exhaustively. For example, TBHP-mediated cyclization of the corresponding 2-biphenylmethanols or 2-biphenylmethylamines[170], or additional methods for regioselective late-stage halogenation[184] of fluorenones such as **242** have not been attempted. However, even in the unlikely event of success, the results would still most likely pale in comparison to existing total synthesis for azafluoranthenes[67, 185], therefore no further research in this area was conducted.

4.3 Synthesis of 4-azafluorenones

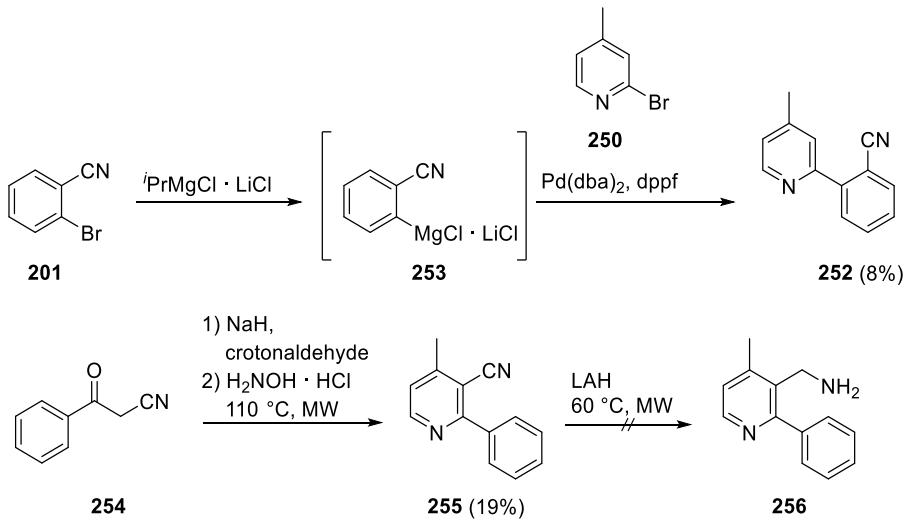
4.3.1 Attempts at the synthesis of 4-azafluorenones *via* 2-(pyridine-2-yl)-benzylamines

The developed methodology for the TBHP-mediated cyclization towards fluorenones was to be employed for the synthesis of structurally related 4-azafluorenones. First, synthesis of onychine (**86**) as the simplest representative of this alkaloid class was attempted, following the same route employed for the synthesis of fluorenones. Therefore, 2-bromo-4-picoline (**250**) was reacted with 2-cyanophenylboronic acid (**251**) under standard Suzuki conditions. Surprisingly, the reaction did not work at all as depicted in Scheme 48. Attempts at reaction optimization were not conducted at this point.



Scheme 48: Attempted synthesis of biaryl **252** *via* Suzuki coupling.

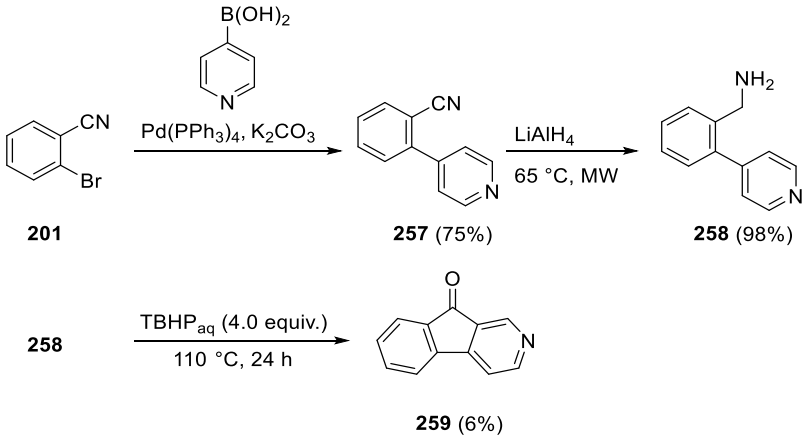
Heinrich von Köller conducted his Bachelor's thesis on this very topic in the Bracher group.[186] Various attempts at finding suitable reaction conditions for this reaction were made. The focus was hereby placed on transition metal-catalyzed cross-coupling reactions. The most successful attempts are depicted in Scheme 49. 2-Bromobenzonitrile (**201**) was reacted with the Turbo-Grignard reagent to generate arylmagnesium bromide **253** *in situ* and reacted with 2-bromo-4-picoline (**250**) under Kumada conditions to give the desired product **252** with a low yield of 8%. In a second approach, the pyridine ring was constructed *via* Michael addition and subsequent intramolecular pyridine condensation. Crotonaldehyde was herefore reacted with benzoylacetonitrile (**254**) under basic conditions. Hydroxylammonium chloride was then added to the *in situ* generated Michael product to give the 2-phenyl-3-cyanopyridine (**255**) in a yield of 19%. This reaction proceeded more smoothly under microwave irradiation, heating in an oil bath only gave the product **255** in a yield of 8%. However, subsequent nitrile reduction of compound **256** with LAH failed.



Scheme 49: Synthesis of pyridylbenzonitrile **252** and 3-cyano-2-phenyl-4-picoline (**255**) by von Köller.[186]

Interestingly, TBHP-mediated cyclization of primary amine **258**, accessible by the standard Suzuki coupling/nitrile reduction two-step synthesis, only gave the corresponding 2-azafluorenone (**259**) in a yield of 6% (Scheme 50). It was unclear at this point if the TBHP-mediated cyclization of primary benzylamine precursors was incompatible with pyridine ring radical acceptor moieties. Since I did not supervise this thesis further details are omitted. Von

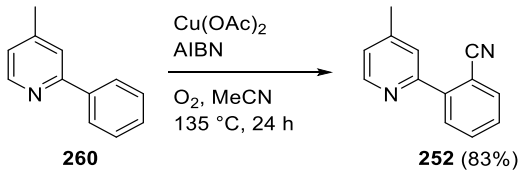
Köller's work ties directly into the topic of this thesis, so discussion of relevant parts seemed essential.



Scheme 50: Synthesis of 2-azafluorenone (**259**) by von Köller.[186]

Von Köller's work serves to illustrate that the necessary precursors for synthesis of 4-azafluorenones are not as readily available as one might expect. The synthetic route developed to prepare a number of fluorenone precursors (Section 4.1) could therefore not be applied to the synthesis of 4-azafluorenones despite their remarkably similar structure.

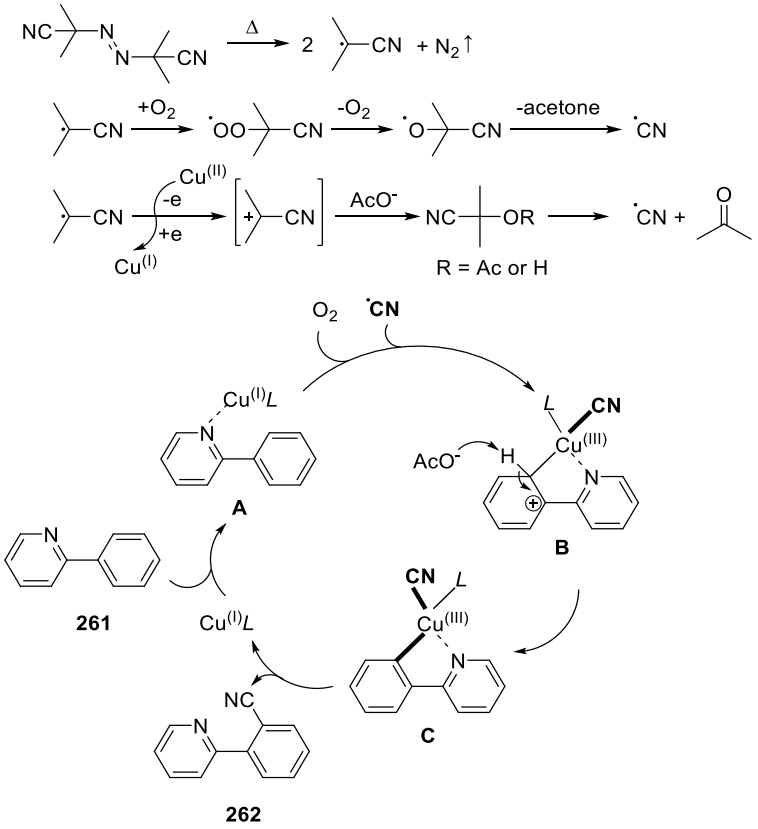
Further optimization of the most promising reaction conditions for the synthesis of suitable precursors presented in von Köller's thesis might have yielded good results. However, moving forward, a third synthetic strategy was attempted instead. While transition metal-catalyzed coupling of 2-bromo-4-picoline (**250**) with 2-cyanophenylboronic acid (**251**) evidently failed, cross-coupling reactions of 2-bromo-4-picoline (**250**) with the unsubstituted phenyl boronic acid to give 2-phenyl-4-picoline (**260**) have been reported in the literature in high yields.[187] Subsequent *ortho*-cyanation leads to the desired precursor **252**. In fact, Xu et al. described a methodology that allows for this exact cyanation, where pyridylbenzonitrile **252** was afforded in a yield of 83% (Scheme 51).[188]



Scheme 51: Synthesis of pyridylbenzonitrile **252** reported by Xu and coworkers.[188]

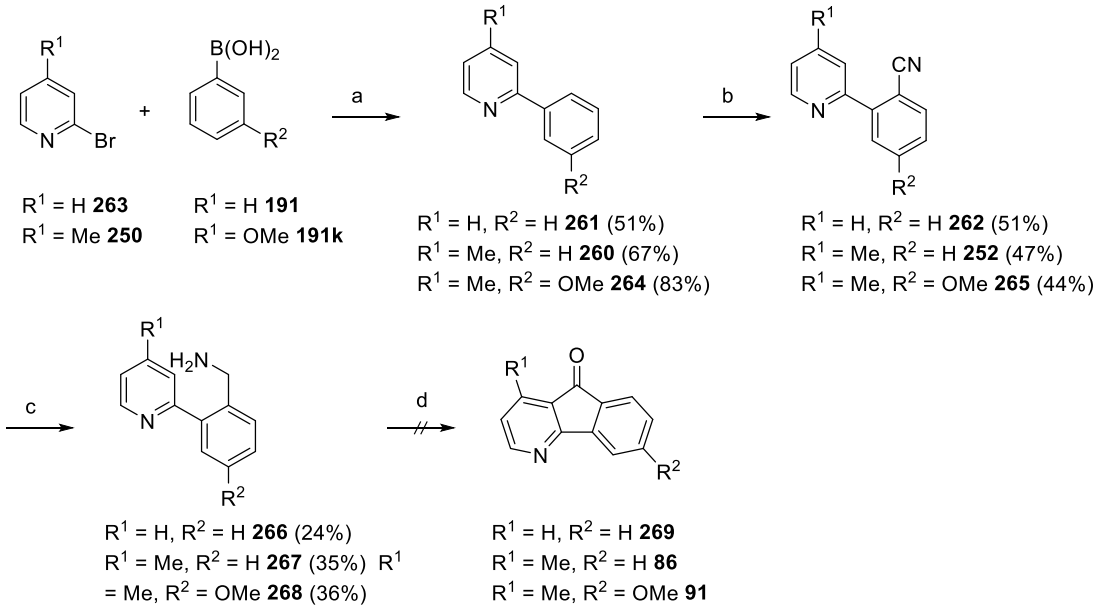
The reaction employs 2,2′-azobisisobutyronitrile (AIBN), which functions both as a cyano radical source[189] and a reducing agent to generate the catalytically active $Cu^{(I)}L$ precatalyst (Scheme 52). The $Cu^{(I)}L$ species coordinates to the pyridine nitrogen of the substrate **261** to form complex **A**. Oxidative addition of complex **A** and a cyano radical generates the high-

valent $Cu^{(III)}$-complex **B** which then isomerizes to transient complex **C** after a rearomatization step. Finally, reductive elimination affords the product and regenerates the $Cu^{(I)}L$ precatalyst.



Scheme 52: Proposed mechanism for the Cu-mediated cyanation of 2-aryl pyiridne (**261**) with AIBN.[188]

To put this method to the test, three model 4-azafluorenones **86**, **269** and **270** were to be prepared. Following standard Suzuki coupling of 2-bromopyridine (**263**) or 2-bromo-4-picoline (**250**) with the respective phenylboronic acids **191** and **191k** gave 2-phenylpyridine (**261**) and two 2-phenyl-4-picolines **260** and **264**. The biaryls where then cyanated, employing the methodology of Xu et al.[188], affording the nitriles **262**, **252** and **265** in yields ranging from 44% to 51% (Scheme 53).



Scheme 53: Attempted synthesis of model 4-azafluorenones. Conditions: a) K_2CO_3, $Pd(PPh_3)_4$, DMF/H_2O (1:1), 100 °C, 18 h; b) AIBN, $Cu(OAc)_2$, O_2, MeCN, 135 °C, 24 h; c) LAH, $AlCl_3$, THF, 0 °C ⟶ rt, 18 h; d) $TBHP_{aq}$, 1,2-DCE, 100 °C, 18 h (yields in parentheses).

The yields reported for the cyanation of nitrile **262** and **252** by Xu et al. (80% and 83% respectively) could not be replicated with the equipment used. The experimental protocol calls for the use of a Schlenk tube as the reaction vessel. However, a large amount of pressure builds as AIBN thermally decomposes and releases nitrogen gas, necessitating a pressure tube even for small batch sizes. In fact, the 20 mL pressure tubes commonly used in the Bracher laboratories only withstood about 5.0 mmol of AIBN at a time before the sealing ring would burst. Reactions could therefore not be scaled-up to a comfortable batch size and had to be carried out multiple times to gather enough product for the next step. Furthermore, these pressure tubes were not of the Schlenk variety and did not allow for a clean exchange of atmosphere. A pure O_2 atmosphere could therefore not be guaranteed which could explain the drop in yield compared to the published work. While it might have been appropriate to find a more practical solution in the long run, like running the reactions in a pressure resistant autoclave that allowed for a clean exchange of atmosphere, the yields of the cyanation reactions were deemed acceptable for the synthesis of model compounds at this point.

The three nitriles **262**, **252** and **265** were then reduced with LAH and $AlCl_3$ to furnish the corresponding primary amines **266**, **267** and **268** as black oils with yields ranging from 24%-36%. Surprisingly, despite some minor amounts of remaining impurities, the NMR spectra of these amines appeared relatively clean, unlike what their unusual appearance might suggest. The ^{1}H NMR-spectrum for **267** is shown in Figure 6 for reference.

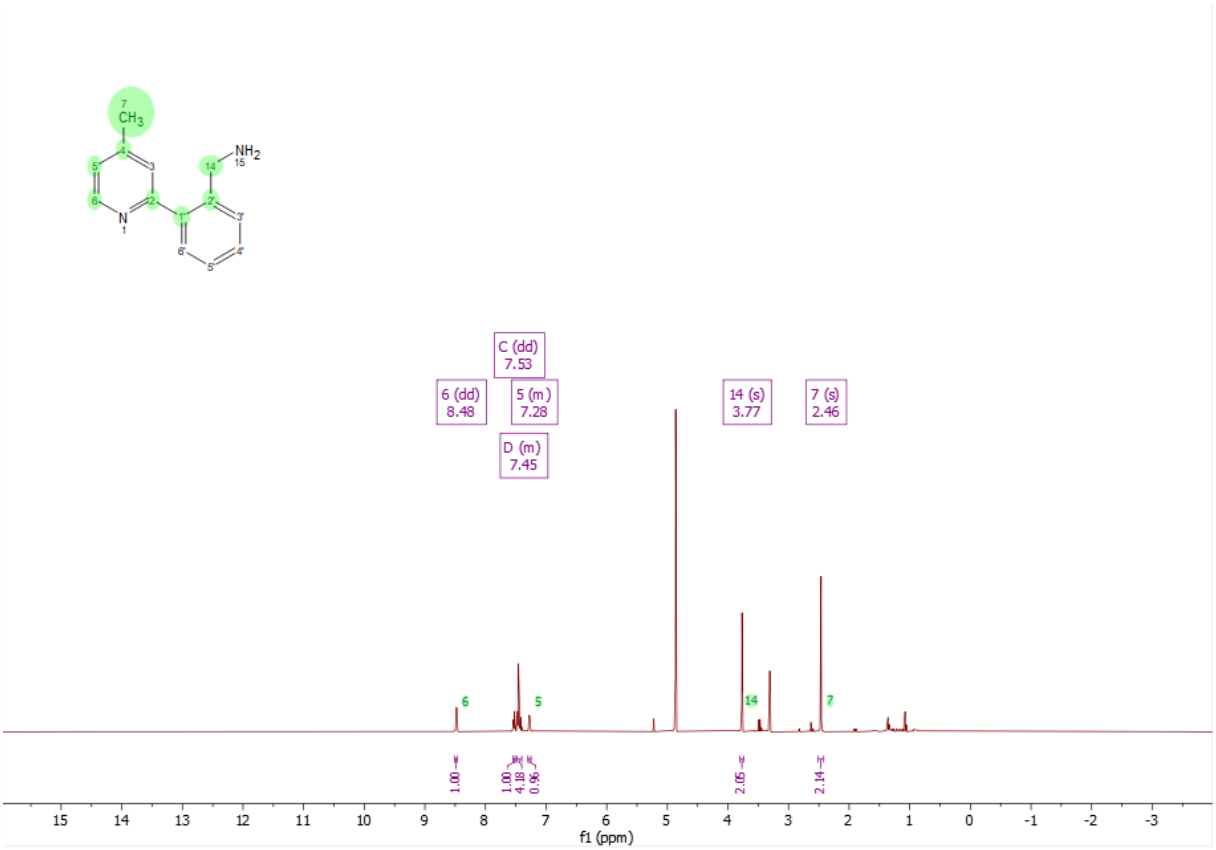
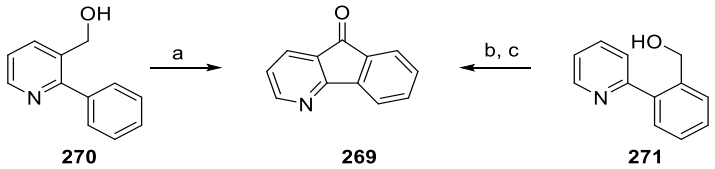


Figure 6: ^{1}H NMR of amine **267**.

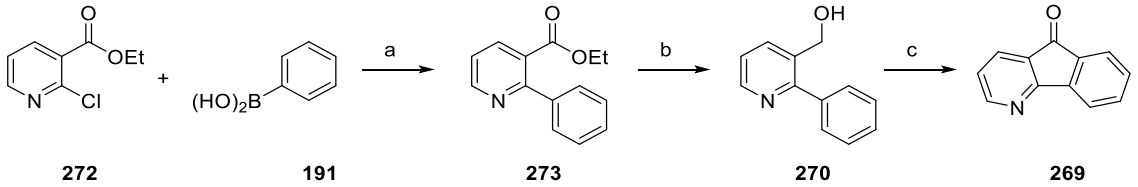
Still, the yields were noticeably lower in comparison with other nitrile reductions performed. Chaitanya et al. reported a yield of 87% for the reduction of nitrile **264** to amine **265** with LAH.[190] Seeing as the NMR spectra of the amine compounds **266**, **267** and **268** were relatively clean, TBHP-mediated cyclization was attempted before further reaction optimization for the precursors. Unfortunately, none of the three amines gave the desired 4-azafluorenones **86**, **91** and **269** upon reaction with aqueous TBHP. These findings corroborate the previously presented synthesis of 2-azafluorenone (**259**) *via* TBHP-mediated cyclization of amine **258** conducted by von Köller as part of his Bachelor's thesis (Scheme 50) where the product **259** was furnished with a yield of only 6%. Based on these experiments, it was concluded that 2-(pyridine-2-yl)benzylamines are not suitable substrates for the TBHP-mediated cyclization towards 4-azafluorenones.

Laha et al. previously reported the synthesis of 4-azafluorenone **269** *via* TBHP-mediated cyclization of both isomeric pyridinemethanol **270**[191] and benzyl alcohol **271.**[133] Interestingly, cyclization of pyridinemethanol **270**, where the benzene ring acts as the radical acceptor, gave 4-azafluorenone (**269**) in a considerably higher yield (90%) than benzyl alcohol **271** under comparable conditions (60%), where the pyridine ring fulfills this role. The cyclization yield of benzyl alcohol **271** could be increased to 76% by employing TBAI as an additive.[133]



Scheme 54: Synthesis of 4-azafluorenone (**269**) reported by Laha et al. Conditions: a) TBHP (8.0 equiv.), 1,2-DCE, 100 °C, 30 h, 90%[191]; b) TBHP (4.0 equiv.), 1,2-DCE, 100 °C, 24 h, 60%[133]; c) TBHP (4.0 equiv.), TBAI (5 mol%), 1,2-DCE, 100 °C, 24 h, 76%[133]. *Note:* No information on the solvent in which TBHP was diluted was given.

The synthesis *via* pyridinemethanol **270** was reproduced to verify its validity (Scheme 55). To this end, commercially available ethyl 2-chloronicotinate (**272**) was reacted with phenylboronic acid (**191**) under Suzuki conditions to give the biaryl **273**. The $Pd(OAc)_2$/SPhos precatalyst system was employed as SPhos ligands confer a high degree of reactivity towards Suzuki cross-couplings even when using otherwise less reactive aryl chlorides.[192] Still, with 40%, the yield was rather low. This synthesis has been reported with yields of up to 95%.[193] Reaction optimization may have yielded better results, but as enough product was furnished to continue, no such attempts were made.



Scheme 55: Synthesis of 4-azafluorenone (**269**). Conditions: a) $Pd(OAc)_2$, SPhos, K_2CO_3, DMF/H_2O (1:1), 100 °C, 18 h, 40%; b) LAH, THF, 0 °C ⟶ rt, 18 h, 54%; c) $TBHP_{dec}$, 1,2-DCE, 100 °C, 30 h, 41%.

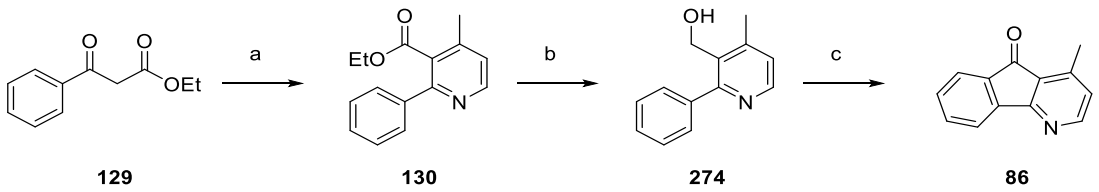
Ester reduction with LAH and $AlCl_3$ gave the pyridinemethanol **270**. While still moderate in yield (54%), this was an improvement over the nitrile reductions for the synthesis of 2-(pyridine-2-yl)benzylamines previously discussed (24-36%). Cyclization of pyridinemethanol **270** with 4.0 equivalents of TBHP gave 4-azafluorenone (**269**) in a yield of 41% after 30 h. The starting material had been completely consumed under these conditions, so the reaction was not further optimized.

4.4 Total synthesis of 4-azafluorenone-type natural products

4.4.1 Total synthesis of onychine and establishment of a proof of concept for the synthesis of 5-oxygenated azafluorenones

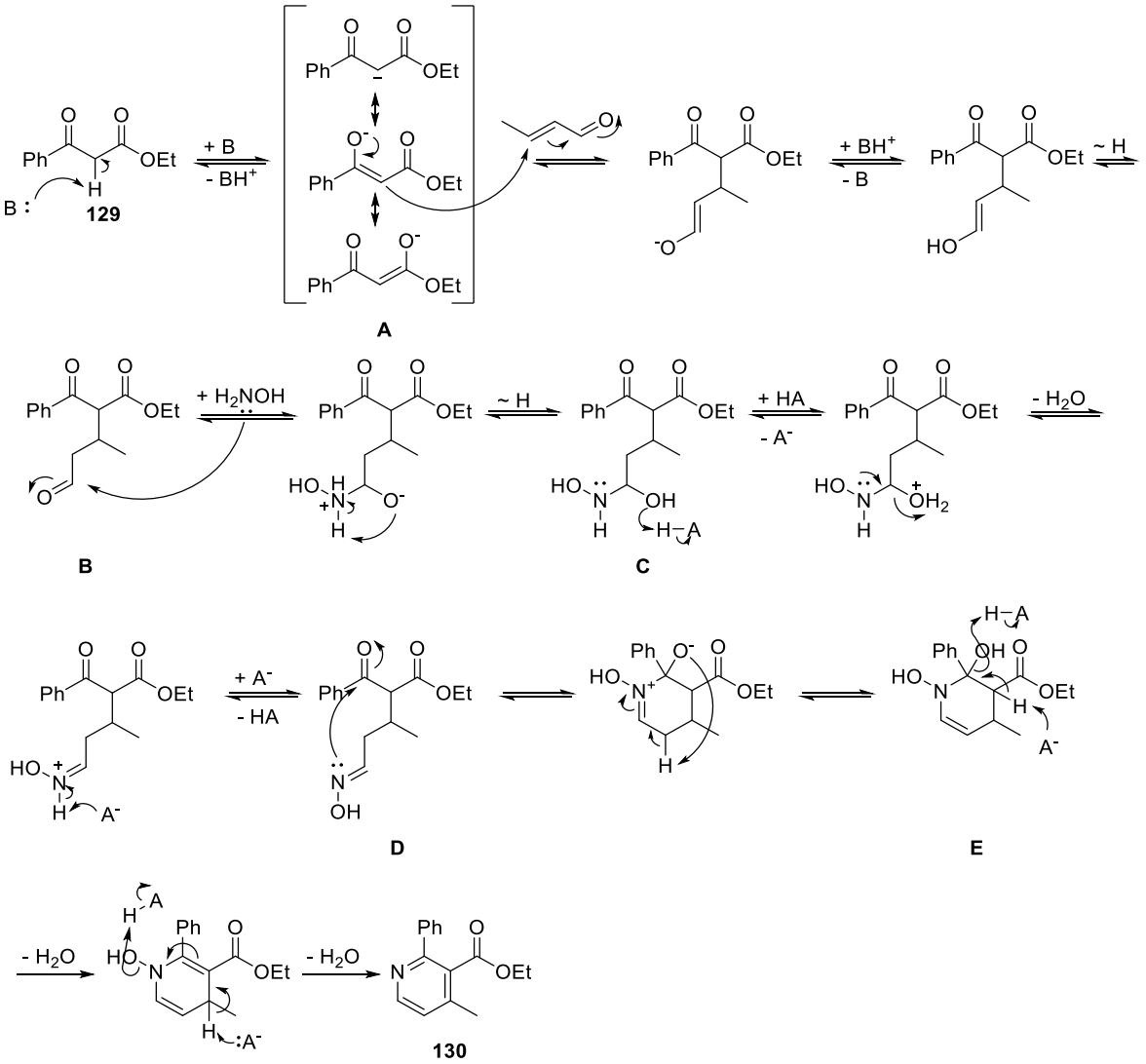
Having confirmed (3-hydroxymethyl)-2-phenylpyridines as suitable precursors for the TBHP-cyclization towards 4-azafluorenones, the next goal was the synthesis of 4-azafluorenone natural products, starting with their simplest representative, onychine (**86**). Although the structure of onychine (**86**) only differs by a single methyl group at C-1 from 4-azafluorenone (**269**), the Suzuki cross-coupling in the first step of the synthesis shown in Scheme 55 could not be employed again, as different from ethyl 2-chloronicotinate (**272**), the required 4-methylnicotinate precursor was not commercially available.

Instead, 2-phenylnicotinate **130** was prepared as described in a previous work of the Bracher group for the synthesis of onychine (**86**).[135] For this purpose, construction of the pyridine ring was achieved *via* base-catalyzed Michael addition of commercially available β-ketoester **129** to crotonaldehyde, followed by intramolecular condensation of the *in situ* generated 1,5-dicarbonyl compound with hydroxylammonium chloride (Scheme 56).



Scheme 56: Synthesis of onychine (**86**). Conditions: a) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min, 40%; b) LAH, THF, rt, 16 h, 65%; c) $TBHP_{non}$, 1,2-DCE, 100 °C, 30 h, 55%. Total yield: 14% over three steps.

A plausible mechanism for this reaction is shown in Scheme 57. The relatively high C-H acidity of β-ketoester **129** (pK_A ~ 11) allows for facile deprotonation by benzyltrimethylammonium hydroxide (triton B) generating enolate ion **A**. The base is later recovered as depicted in the mechanism, so only catalytic amounts thereof are necessary. Michael addition of enolate **A** to crotonaldehyde gives the 1,5-dicarbonyl compound **B** following prior keto-enol tautomerization.

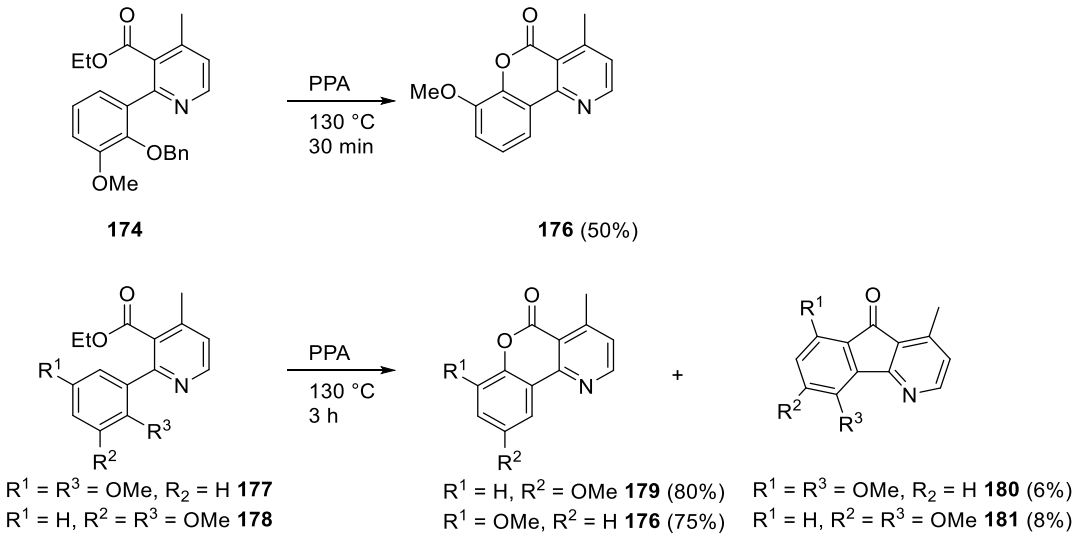


Scheme 57: Plausible mechanism for the synthesis of nicotinate **130**.

Upon addition of hydroxylamine (as hydroxylammonium chloride) and AcOH, aldoxime **D** is ultimately formed *via* condensation, following elimination of water from *N*-hydroxy hemiaminal **C**. Due to the difference in their respective steric hindrance, and electron donor resonance interactions of the ester's ethoxy group, hydroxylamine primarily reacts with the aldehyde functional group, although side reactions with the ketone group are conceivable to a lesser degree. In a similar manner, nucleophilic attack of aldoxime **D** at the ketone group leads to cyclic *N*-hydroxy hemiaminal **E**. Again, side reactions with the ester group are possible although it is less reactive than the ketone group. The driving force behind the subsequent ring oxidation is the generation of an aromatic system *via* elimination of water. The fully aromatized nicotinate ester **130** is furnished by using hydroxylammonium chloride (Knoevenagel conditions[194]) which facilitates the elimination of an additional molecule of water, rather than ammonia (Hantzsch conditions) which would give the Hantzsch dihydropyridine instead.

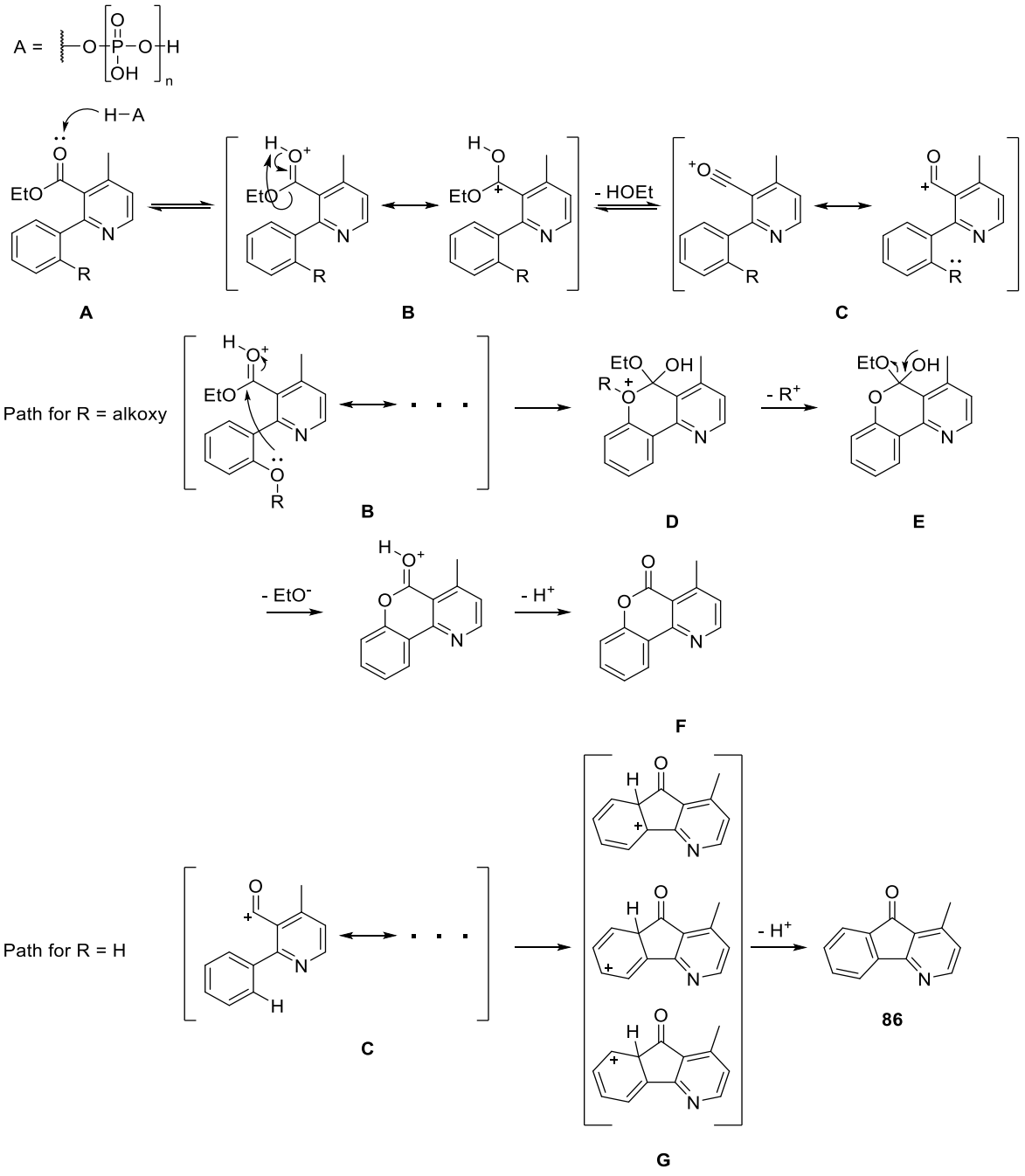
Nicotinate ester **130** was then reduced with LAH to afford pyridinemethanol **274** in 65% yield (Scheme 56). TBHP-mediated cyclization was performed in both aqueous TBHP and TBHP diluted in *n*-decane under heating to 100 °C for 30 h. Reaction with the former furnished the alkaloid onychine (**86**) in 30% yield while the latter gave onychine (**86**) in 55% yield. This confirmed the previous findings that TBHP-mediated cyclization with substrates bearing oxygen containing functional groups as the reactive center, such as alcohols and aldehydes, performed better in TBHP diluted in alkanes rather than aqueous TBHP. From this point forward, TBHP diluted in *n*-nonane or *n*-decane was used for cyclization of 3-hydroxymethyl-2-phenyl-4-picolines.

Having successfully established a new route for the total synthesis of the natural product onychine (**86**), unsuccessful attempts at total synthesis of congeners thereof in previous works of Franz Bracher labeled as dead ends were reexamined. As previously discussed (Section 2, Scheme 19 and Scheme 20), conventionally employed thermal Friedel-Crafts-type cyclization of nicotinate esters with alkoxy residues in *ortho*-position at the phenyl ring in strongly acidic media yield lactones as the major product, while the desired 4-azafluorenones are furnished only in very low yields if at all (Scheme 58).



Scheme 58: Lactonization of nicotinate esters **174**, **177** and **178** bearing alkoxy residues in *ortho*-position at the phenyl ring reported by Zhang et al.[87] and Bracher.[151]

A plausible mechanism for both the acid-catalyzed intramolecular Friedel-Crafts-type acylation and the intramolecular lactonization of 2-arylnicotinate esters **A** with PPA are shown in Scheme 59. Other suitable alternatives to PPA include HF, sulfuric acid, phosphoric acid and methanesulfonic acid.[195]

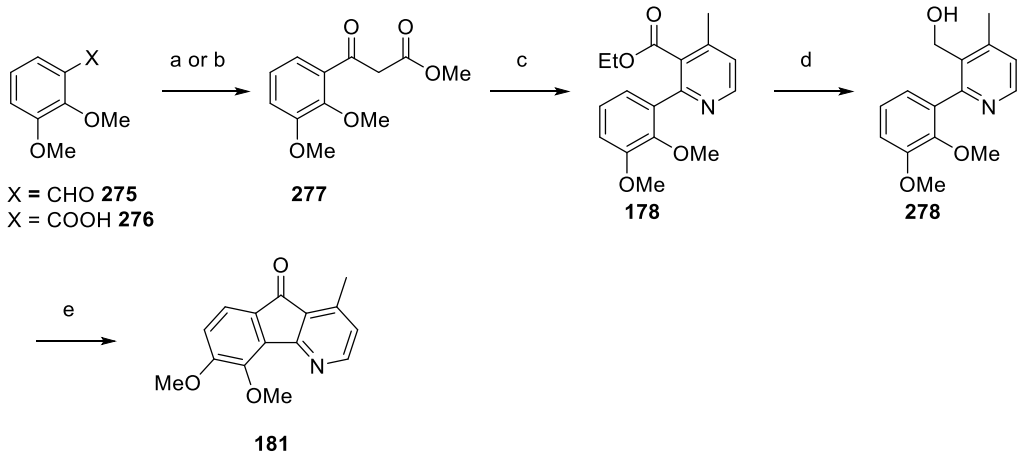


Scheme 59: Plausible mechanisms of the acid catalyzed intramolecular Friedel-Crafts-type acylation and lactone formation.

Many intramolecular Friedel-Crafts-type reactions of this nature are performed with carboxylic acids or acyl chlorides. Although less common, esters are also suitable substrates. The reaction is hereby facilitated by its intramolecular nature. The reactive moieties are always in close vicinity, meaning their effective concentration is increased considerably. Prior ether cleavage of the alkoxy group under these conditions can be ruled out as part of the mechanism, as numerous PPA-mediated cyclizations of nicotinate esters towards 4-azafluorenones with methoxy substituents in different positions remaining intact have been reported. The protonated ester **B** or the thereof derived acylium ion **C** act as potent electrophiles.

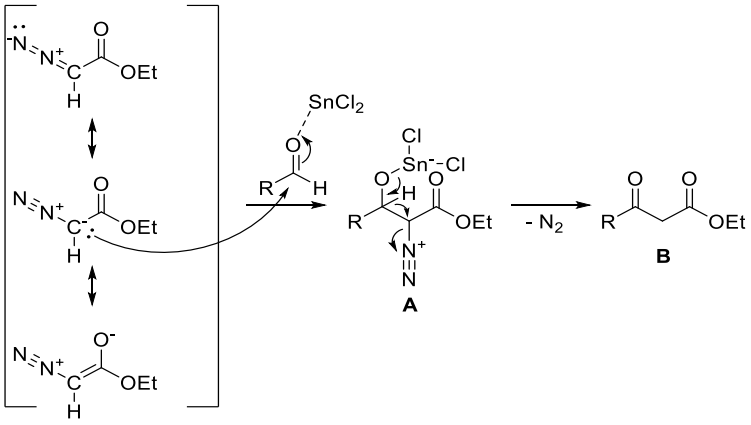
Alternatively, the reaction may proceed in a similar manner after acidic ester hydrolysis. Historically, Friedel-Crafts acylations employ Lewis acids such as ferric chloride, iron, iodine or zinc chloride iron in stoichiometric amounts which coordinate to the carbonyl group and promote the generation of the acylium ion intermediate, therefore accelerating the rate of acylation and increasing the yield. At high temperatures however, good yields have been reported even in absence of Lewis acid catalysts for sufficiently active aromatic nuclei.[196] Nucleophilic attack of the alkoxy group's oxygen lone pair at the positively polarized carbon atom of either **B** or **C** ultimately leads to a tertiary oxonium cation intermediate **D**, from which the intermediate **E** is furnished, and finally lacton **F** following elimination of ethoxide ion. Alkoxy residues were singled out as substituents leading towards non-Friedel-Crafts-type cyclization products, however it is easy to imagine similar reactions occurring with other nucleophilic residues bearing lone pairs, such as phenols, thiophenols, thioethers or amines. In absence of an alkoxy group in *ortho*-position at the phenyl ring, however, the phenyl ring attacks the positively polarized carbon center through an electrophilic aromatic substitution. The resulting Wheland-complex **G** is rearomatized *via* deprotonation and provides the 4-azafluorenone (**86**). The mechanism for this pathway was portrayed with the acylium ion **C** as the electrophile out of convenience.

So far, a proof of concept for the TBHP-mediated cyclization of 3-hydroxymethyl-2-phenyl-4-picolines as a viable alternative for the synthesis of onychine (**86**) *via* intramolecular Friedel-Crafts-type acylation of nicotinate esters has been established (Scheme 57). However, it was still uncertain if this method would allow preparation of 5-oxygenated 4-azafluorenones instead of furnishing the lactones like it is the case for the latter. 5,6-Dimethoxyonychine (**181**) was chosen as the model compound to answer this question (Scheme 60).



Scheme 60: Total synthesis of 5,6-dimethoxyonychine (**181**). Reaction conditions: a) $SnCl_2$, ethyl diazoacetate, DCM, rt, 1 h, 38% (from **275**); b) first ethyl potassium malonate, $MgCl_2$, NEt_3, EtOAc, 0 °C → 35 °C, 6 h, then RCOCl derived from **276** ($SOCl_2$, 2 h, reflux), 0 °C → rt, 18 h, 67%; c) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min, 57%; d) LAH, THF, rt, 16 h, 67%; e) $TBHP_{non}$, 1,2-DCE, 100 °C, 18 h, 24%.

Compared to the synthesis of onychine (**86**), most of the β-ketoesters required as building blocks for the synthesis of higher substituted azafluorene alkaloids are not commercially available. Classic methods for the preparation of β-ketoesters include reactions such as the crossed Claisen condensation. However, the respective acetophenone and benzoate precursors themselves are also seldom commercially available and have to be prepared first. This is usually accomplished by reacting aldehyde starting materials with organometallic methylation reagents and subsequent oxidation of the resulting secondary alcohol in case of the former or Fischer esterification of benzoic acid starting materials in case of the latter.[197] Instead, the method of Holmquist and Roskamp[198] was employed initially, which allowed for direct preparation of β-ketoesters from aldehydes. This method of preparation was also used for the Bracher synthesis of the alkaloid 6-methoxyonychine (**91**) and its unnatural congener 8-methoxyonychine (**164**) and was therefore already well-established in the Bracher group.[199] A plausible mechanism is depicted in Scheme 61.



Scheme 61: Plausible mechanism for the preparation of β-keto esters from aldehydes with $SnCl_2$ and EDA.

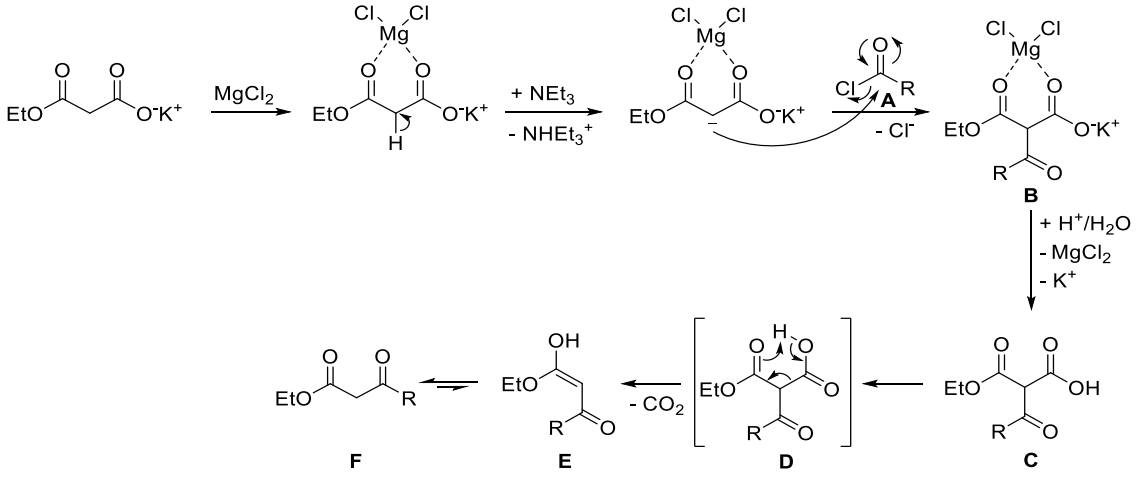
Tin(II) chloride-mediated Lewis acid catalysis facilitates addition of ethyl diazoacetate (EDA) to the carbonyl group of the aldehyde. Bandyopadhyay and coworkers suggest a β-hydroxy-α-diazo ester intermediate **A** that is converted to the β-ketoester **B** following 1,2-hydride shift and elimination of nitrogen.[200]

However, as noted by Holmquist and Roskamp, this reaction is considerably more efficient with aliphatic aldehydes than with aromatic aldehydes. For example, reaction of an equimolar mixture of EDA, benzaldehyde and 3-phenylpropionaldehyde gave a 30:1 ratio of β-ketoesters in favor of the latter. Yields reported for aromatic aldehydes yield are around 35-50%. This matches the yield of 38% that β-ketoester **277** was furnished in with this method starting from 2-3-dimethoxybenzaldehyde (**275**). In fact, a significant portion of the starting material was not consumed, even upon further addition of EDA. Furthermore, the R_f-values of both aldehyde and β-ketoester were very similar, with the β-ketoester also eluting in wide bands/smears from

the flash chromatography column, complicating isolation efforts, especially on large reaction scales. Often a crude mixture of aldehyde starting material and β-ketoester had to be used for the following reaction when β-ketoesters were synthesized with this procedure. For this reason, alternative methods for the preparation of β-ketoesters were explored.

Yadav and coworkers reported a similar method.[201] Hereby the aldehyde substrate is reacted with EDA and $NbCl_5$ in DCM at room temperature. The mild Lewis acid $NbCl_5$ is hereby used as a substitute for $SnCl_2$ employed in the Roskamp method, also activating the aldehyde for nucleophilic attack by complexation. High yields for electron-rich, electron-deficient, acid sensitive aromatic and aliphatic aldehydes were reported. Side-by-side comparison of TLCs of both methods, however, seemed to reveal little to no difference for the electron-rich aromatic aldehyde substrates tested in this project.

The method reported by Clay et al. uses $MgCl_2$, NEt_3 and ethyl potassium malonate to convert acyl chlorides to the β-ketoesters.[202] The choice of solvent hereby depends on the substrate. Aromatic acyl chlorides with electron-withdrawing substituents give better yields in MeCN (method A) while ethyl acetate is more suitable for electron rich aromatic acyl chlorides (method B). Reaction of 2,3-dimethylbenzoic acid (**276**) upon prior conversion to the acyl chloride gave the corresponding β-ketoester **277** in a yield of 67% following method B. In contrast with Roskamp's protocol, Clay's protocol reports high yields for the synthesis of aromatic β-ketoesters and allows the preparation of large-scale batches. Furthermore, unreacted starting materials (or rather their hydrolysis products, the carboxylic acids) and products significantly differ in their R_f-values, simplifying isolation procedures. A plausible mechanism for this reaction is shown in Scheme 62.



Scheme 62: Plausible mechanism for the preparation of β-ketoesters from *in situ* generated acyl chlorides with $MgCl_2$, NEt_3 and ethyl potassium malonate.

Diethyl malonate employed in older protocols for the preparation of β-ketoesters can lead to several byproducts like the methyl ketone in case both ester groups are hydrolyzed or

conversely, the acylated diethyl malonate intermediate if both ester groups remain unhydrolyzed.[202] Ethyl potassium malonate lowers the risk thereof by substituting one of diethyl malonate's ester groups with a carboxylate salt. Metal complexation of the 1,3-dicarbonyl system by the bivalent Lewis acid $MgCl_2$ increases the methylene groups acidity to the point where NEt_3 is capable of deprotonation. The magnesium malonate complex can then be acylated by acid chloride **A** to give intermediate **B**. Although not reflected in the mechanism, 2.0 equivalents of base are required for the reaction to proceed efficiently. This is because the intermediate **B**, bearing an additional electron withdrawing substituent is a stronger acid than the starting material and can therefore neutralize a portion of the enolate.[203] The base has to generate the enolate quantitatively while not reacting with the acyl chloride, two conditions the $MgCl_2$-NEt_3 base system meets. During acidic work-up the magnesium complex **B** is liberated to give the β-keto acid **C**. β-Keto acids are prone to decarboxylation at elevated temperatures *via* a six-membered cyclic, concerted transition state **D**. Introduction of an additional anion stabilizing ketone substituent adjacent to the reactive β-carbon center presumably enables decarboxylation to occur even at close to ambient temperature. The resulting enol **E** tautomerizes to the keto form **F**.

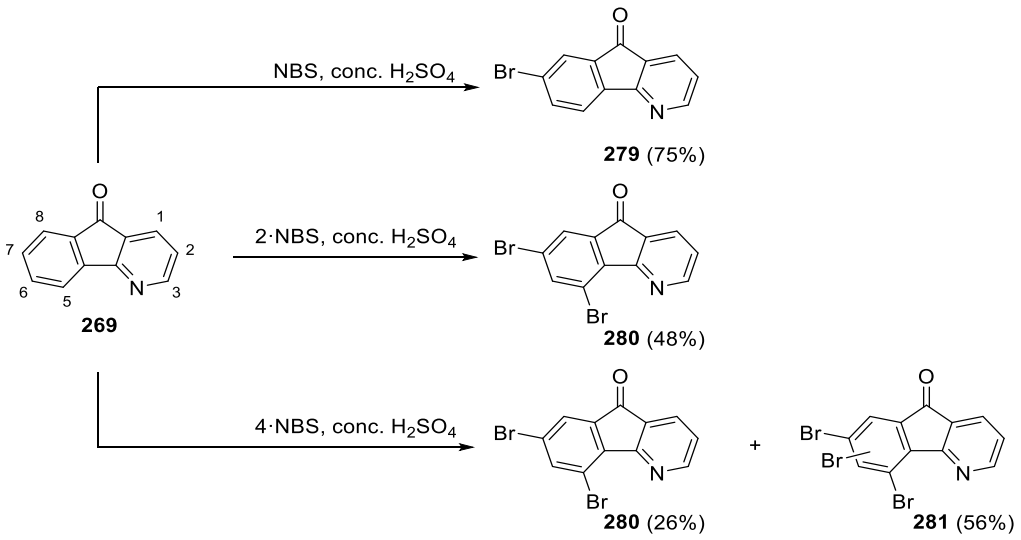
Most β-ketoesters used as intermediates for the synthesis of 4-azafluorenone alkaloids discussed from this point onward were prepared using both Roskamp's and Clay's methods so long as the appropriate starting materials were commercially available. Moving forward, only the method that gave the higher yield will be mentioned for the total synthesis of the respective alkaloids. A tabular comparison of both methods for each β-ketoester can be found in Section 4.5.

Construction of the pyridine ring from β-ketoester **277** gave nicotinate ester **178** in a yield of 57% (Scheme 60). Reduction of the ester with LAH yielded the pyridinemethanol **278** in 67% yield. TBHP-mediated cyclization was carried out with 8.0 equivalents of both aqueous TBHP and TBHP diluted in *n*-decane for 30 hours. The former gave azafluorenone **181** in 10%, the latter in 24% yield. While the yield was somewhat lower than expected, TBHP-mediated radical cyclization did not yield any lactones. Thus, a new synthetic route towards the total synthesis of 5-oxygenated 4-azafluorenones had been established.

4.4.2 Total synthesis of darienine

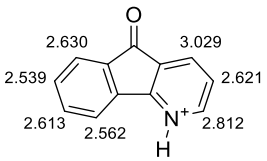
Incidentally, 5,6-dimethoxyazafluorenone (**181**, Section 4.4.1, Scheme 60) further served as an intermediate towards the natural product darienine[75a] (**99**). Młochowski and Szulc reported on the bromination patterns of monoazafluorenones and diazafluorenones (Scheme 63).[204] Reaction of NBS with 4-azafluorenone (**269**) in an equimolar ratio in H_2SO_4 at 45–50 °C for 1–2 h gave the 7-bromo derivative **279** as the sole regioisomer in 75% yield after basic work-up.

A molar ratio of 2:1 NBS to starting material afforded the 5,7-dibromo derivative **280** in 48% yield, meanwhile a ratio of 4:1 gave a mixture of the disubstituted compound **280** (26%) and trisubstituted 4-azafluorenones **281** (56%). Employment of bromine (Br_2) as the bromination agent required more severe conditions to react with azafluorenones (24–72 h, autoclave, temperatures above 145 °C). On the practical side, NBS is also easier to portion than bromine, especially for small-scale reactions and therefore reduces the risk of adding bromine source in substoichiometric or excess amounts which could lead to a mixture of mono- and dibromoazafluorenones. In strongly acidic medium like H_2SO_4, NBS is thought to liberate electrophilic bromine cations, which are attacked by the benzene ring of the azafluorenone in an electrophilic aromatic substitution.



Scheme 63: Bromination pattern of 4-azafluorenone (**269**).[204]

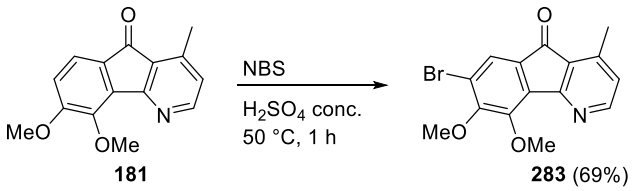
The localization energy values (L_r^+) and π-electron densities (q_r) for the 4-azafluorenone cation **282** were calculated by Młochowski and Szulc *via* the Hückel molecular orbital (HMO) method, which allowed prediction of the order of bromination (Figure 7). The lower the L_r^+-value of the position, the more active the bromination site, which resulted in the following regioselectivity order: C-7 (L_r^+ = 2.539 β), C-5 (L_r^+ = 2.562 β), C-6 (L_r^+ = 2.613 β), C-2 (L_r^+ = 2.621 β), C-8 (L_r^+ = 2.630 β), C-3 (L_r^+ = 2.812 β) and C-1 (L_r^+ = 3.029 β). Perhaps to be expected, the *N*-protonated pyridine ring is far less reactive towards electrophilic aromatic bromination than the phenyl ring. Individual L_r^+-values of the phenyl ring carbons may not seem to differ greatly, however, every experiment conducted by the authors gave clean conversions for mono and dibrominations rather than isomeric mixtures and matched the calculated predictions.



282

Figure 7: Localization energy values (L_r^+) for the 4-azafluorenone cation **282**.[204]

While reactivity could differ somewhat from compound to compound, it was speculated that the general regioselectivity pattern towards electrophiles would be retained across derivatives of 4-azafluorenone (**269**) barring the influence of directing groups in certain positions. C-1, C-5, and C-6 of 5,6-dimethoxyonychine (**181**) are occupied with methyl and methoxy groups, respectively. The two methoxy groups should direct towards both C-7 and C-8. The desired bromination site C-7 also boasts the lowest reported L_r^+-value for the unsubstituted 4-azafluorenone cation **282** (L_r^+ = 2.539 β) while somewhat higher for C-8 (L_r^+ = 2.630 β). And indeed, reaction of 5,6-dimethoxyonychine (**181**) with NBS gave the 7-bromo derivative **283** as the sole regioisomer with a yield of 69% (Scheme 64).



181 **283** (69%)

Scheme 64: Regioselective bromination of 5,6-dimethoxyonychine (**181**).

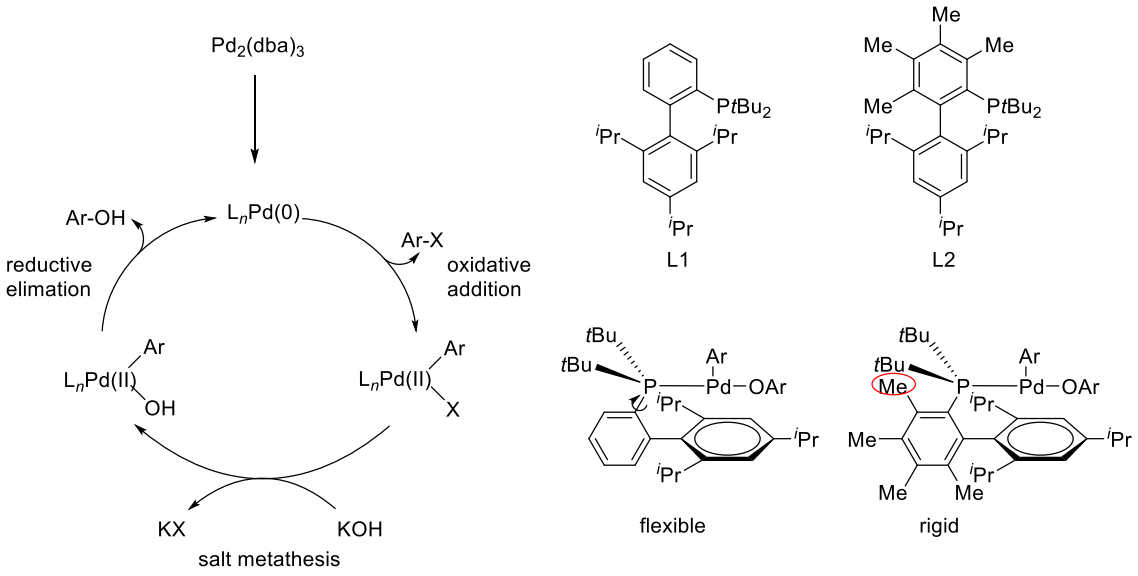
NBS is a commonly employed reagent for the bromination of benzylic and allylic carbons. Undesired formation of the radical substitution product of the benzylic C-1 methyl group was not observed, presumably due the employed reaction conditions not facilitating radical reactions. Radical side chain substitution of 8-methyl-4-azafluorenone with NBS and AIBN in CCl_4 heated to reflux, for example, has been reported to proceed in nearly quantitative yields.[205]

With 7-bromo-5,6-dimethoxyonychine (**283**) in hand, the bromide substituent had to be converted to the phenol in a final step. The Buchwald group developed a Pd-catalyzed synthesis of phenols from aryl halides in excellent yields.[206] Aryl halide, KOH, Pd_2dba_3 and one of two phosphine ligands L1 (*t*BuXPhos) or L2 (Me_4*t*BuXPhos) are hereby reacted in a H_2O/1,4-dioxane (1:1) cosolvent system at 100 °C for 1–18 h and subsequently acidified with hydrochloric acid.

Various functional groups have proven compatible with this reaction, including those related to 4-azafluorenones like methyl ketones and *N*-heterocycles. It was observed, that the smaller *t*BuXPhos ligand L1 gave better yields with sterically hindered substrates bearing di-*ortho*

substituents, while Me$_4$*t*BuXPhos ligand L2 more efficiently assisted in conversion of electron deficient aryl chlorides and heteroaryl halides.

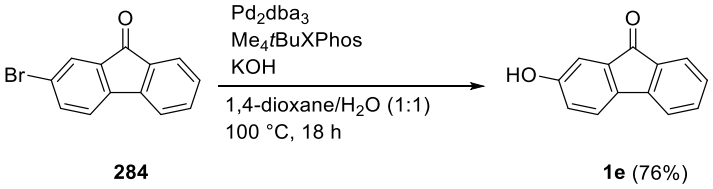
In a closely related report by the same group published a couple of months prior detailing the Pd-catalyzed coupling of phenols with aryl halides, it was described that the bulky phosphine ligands L1 and L2 confer a conformational rigidity to intermediates of the catalytic Pd-cycle that faciltates C-O reductive elimination and thus achieve better results at C-O bond formation than less bulky phosphine ligands such as SPhos or JohnPhos.[207] Coupling of aryl halides with strongly electron-withdrawing or electron-donating *ortho* substituents in particular gave little-to-no yield with more established phosphine ligands. Concerning the difference between the two ligands L1 and L2, the methyl groups on the top ring of L2 are suspected to force the ligand into a certain conformation where the methyl group *ortho* to the phosphorous center acts as a physical divide between the two *tert*-butyl groups, pushing them towards the Pd center to exert their effects on the bound aryl and aryloxide units (Scheme 65, methyl group circled in red). Depending on the substrate, the added bulk of L2 is unnecessary to facilitate reductive elimination and formation of the [LPd(OAr)Ar] intermediate proceeds more smoothly with the sterically less hindered L1. These considerations likely also apply to the conversion of aryl halides to phenols with KOH.



Scheme 65: Suggested catalytic cycle for the Pd-catalyzed hydroxylation of arene halides and effect of methyl substituents on conformational rigidity of ligands L1 and L2.[207]

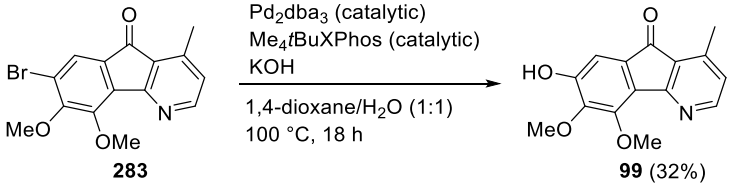
The Pd-catalyzed bromide-to-phenol conversion was first tested on commercially available 2-bromofluorenone (**284**) and gave the corresponding 2-hydroxyfluorenone (**1e**) in a yield of 76% using Me$_4$*t*BuXPhos. Based on the substrate criteria[206] laid out by the Buchwald group, the case could be made for the employment of either of the two ligands. On one hand, onychines are electron-deficient owing to their ketone bridge and pyridine ring substructure, which would suggest use of Me$_4$*t*BuXPhos. On the other hand, this could be offset by recurrent patterns of

onychine congener methoxylation, which may also hinder the ligand sterically, urging towards employment of *t*BuXPhos, although only di-*ortho* substituted substrates seemed to significantly hinder conversion with Me$_4$*t*BuXPhos according to the Buchwald group. Ultimately, Me$_4$*t*BuXPhos was chosen over *t*BuXPhos primarily out of convenience because the former was available in our group's chemical storage at the time while the latter was not.



Scheme 66: Model synthesis for the conversion of bromide **291** to phenol **1e**.

After confirming the validity of the method in a model reaction (Scheme 66), 7-bromo-5,6-dimethoxyonychine (**283**) was converted to the alkaloid darienine (**99**) in a yield of 32% (Scheme 67).



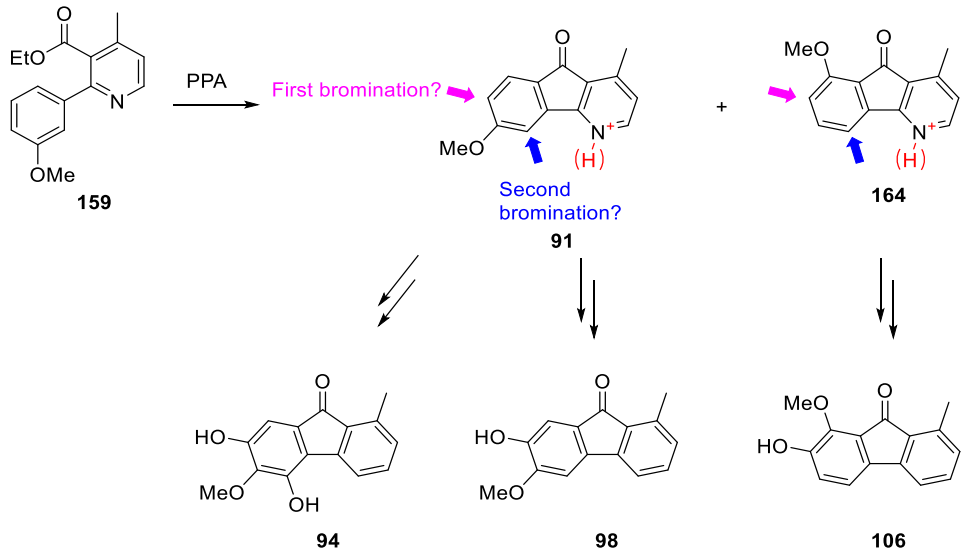
Scheme 67: Bromide-to-phenol conversion of 7-bromo-5,6-dimethoxyonychine **283**. Total yield: 1.4% over six steps from **276**.

The yield was quite low, perhaps *t*BuXPhos would have yielded better results. Having expended **283** in this reaction, the synthesis was, however, not reattempted from the start to improve the yield of the final step. This marks the first published total synthesis of this alkaloid.

4.4.3 Attempts at the total synthesis of cyathocaline, isooncodine and macondine

Having successfully predicted the regioselectivity for the bromination of 5,6-dimethoxyonychine (**181**) based on the model reported by Młochowski and Szulc[204] gave further incentive to explore this late-stage functionalization strategy. Several onychine-type natural products were anticipated to be accessible from appropriately methoxylated 4-azafluorenones by exploiting the regioselectivity of bromination reactions. Based on these considerations, cyathocaline (**94**) and isooncodine (**98**) should be accessible from 6-methoxyonychine (**91**) after regioselective mono- and dibromination at C-7 and C-5 and subsequent bromide-to-phenol conversion, respectively (Scheme 68). However, it was unclear at this point if two bromide residues could be converted to the respective phenolic hydroxy groups at once for the synthesis of cyathocaline (**94**). In the same manner, 8-methoxyonychine (**164**) should give macondine (**106**) unless the methoxy substituent's directing effect favors bromination at C-5 instead of C-7. In theory, both 6-methoxyonychine (**91**) and 8-

methoxyonychine (**164**) should be accessible from a single nicotinate ester precursor **159** if PPA-mediated cyclization thereof doesn't exclusively yield the sterically less hindered isomer 6-methoxyonychine (**91**).

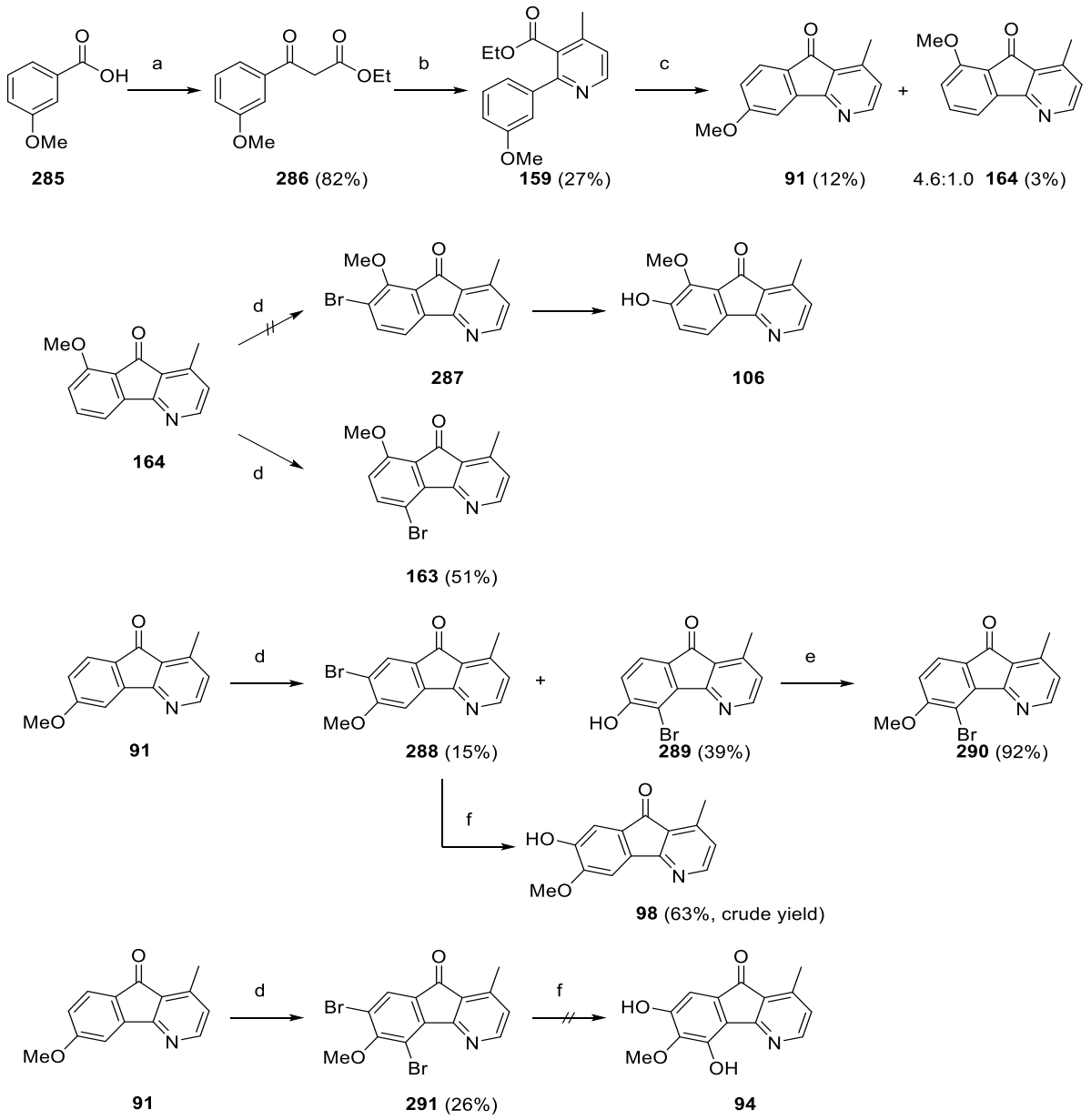


Scheme 68: Predicted outcomes for the bromination of azafluorenone intermediates **91** and **164**.

Commercially available 3-methoxybenzoic acid (**285**) was converted to the β-ketoester **286** with $SOCl_2$, ethyl potassium malonate, $MgCl_2$, and NEt_3 (Scheme 69). Subsequent reaction with crotonaldehyde and hydroxylammonium chloride furnished the nicotinate ester **159**. An isomeric mixture of 6-methoxyonychine (**91**) and 8-methoxyonychine (**164**) was received upon PPA-mediated cyclization (150 °C, 1.5 h) in a ratio of 4.6:1. The yield, however, was exceptionally low with only 15% of cyclization product for both isomers combined.

Arita et al. reported similarly low yields for the PPA-mediated cyclizations of the respective nicotinate esters towards methoxylated onychine derivatives they conducted.[129] Through optimization of reaction time and temperature, the authors were able to increase their yield of PPA-mediated cyclization towards onychine (**86**) from 20% (180 °C, 4 h) to 56% (220 °C, 1 h). Applying these reaction conditions to the synthesis towards 6-methoxyonychine (**91**), however, reportedly only gave the demethylated product 6-hydroxyonychine in a yield of 3%. The yield of demethylated product could be increased to 31% by increasing the reaction time to 4 h. Cyclization of nicotinate ester **159** was also reported by the Snieckus group.[139] The exact reaction conditions were not specified, however, a citation was given for the PPA-mediated cyclization where the substrates were reacted with PPA for 2 h at 215 °C, similar to the conditions employed by Arita and coworkers. Interestingly, the yield for Snieckus' synthesis was quite high (80%), and neither formation of the second regioisomer nor demethylation of the methoxy group were mentioned.

The reaction was performed again at 220 °C for 2 h and gave a mixture of 6/8-methoxy (2%/0.2%) and 6/8-hydroxyonychines (0.2% crude mixture, not separated) in yields even lower than under the conditions previously employed. The results of the Snieckus group could not be replicated. Notably, *O*-demethylation was first observed at this temperature.



Scheme 69: Attempted synthesis of cyathocaline (**94**), isooncodine (**98**) and macondine (**106**). Conditions: a) first ethyl potassium malonate, $MgCl_2$, NEt_3, EtOAc, 0 °C → 35 °C, 6 h, then RCOCl derived from **285** ($SOCl_2$, 2 h, reflux), 0 °C → rt, 18 h; b) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min; c) PPA, 150 °C, 1 h; d) NBS, H_2SO_4 conc., 50 °C, 1 h; e) MeI, K_2CO_3 , DMF, 16 h, rt; f) $Pd_2(dba)_3$, Me_4*t*BuXPhos, KOH, 1,4-dioxane/H_2O (1:1), 18 h, 100 °C (yields given in parentheses).

Bromination of 8-methoxyonychine (**164**) unfortunately gave 5-bromo-8-methoxyonychine (**163**) in 51% yield rather than the desired 7-bromo derivative. In the presence of directing groups at certain ring positions, the reliability of the prediction model based on the 4-azafluorenone cation **282** is therefore called into question (Figure 7). Bromide-to-phenol

conversion of the 5-bromo derivative **263** would have led to 5-hydroxy-8-methoxyonychine which has yet to be isolated from nature. Thus, the reaction was not performed.

Surprisingly, reaction of 6-methoxyonychine (**91**) with one equivalent of NBS gave a mixture of 7-bromo-6-methoxyonychine (**288**) in 15% and 5-bromo-6-hydroxyonychine (**289**) in 39%. This is the only bromination experiment under these conditions (NBS, conc. H_2SO_4, 50 °C, 1 h) where demethylation was observed. Considering that the formation of 7-bromo-6-hydroxyonychine was not observed, it appears that demethylation also induced a change in regioselectivity towards bromination. A methoxy group at C-6 directs towards bromination at C-7, while a hydroxy group at C-6 directs towards C-5 bromination. 7-bromo-6-methoxyonychine (**288**) was subjected to bromide-to-phenol conversion to give the alkaloid isooncodine (**98**; 5 mg of crude product). Unfortunately, purification attempts *via* both preparative TLC and FCC did not yield the pure compound. Larger quantities of crude product would likely facilitate purification and might allow access to pure product *via* this synthesis route. However, as a total synthesis of isooncodine (**98**) had already been developed by the Cavé group[93], renewed attempts were not made. The shift in regioselectivity observed for hydroxylated onychines might warrant further exploration and allow access to more derivatives. Next, 5-bromo-6-hydroxyonychine (**289**) was *O*-methylated. Bromide-to-phenol conversion of 5-bromo-6-methoxyonychine (**290**) would lead to the alkaloid isoursuline (**90**). This reaction was not performed as a more efficient total synthesis of isoursuline (**90**) had already been concluded at that point, which is discussed later (Section 4.4.5, Scheme 76). The NMR spectra of 5-bromo-6-methoxyonychine (**290**) obtained *via* these two respective synthesis routes matched exactly.

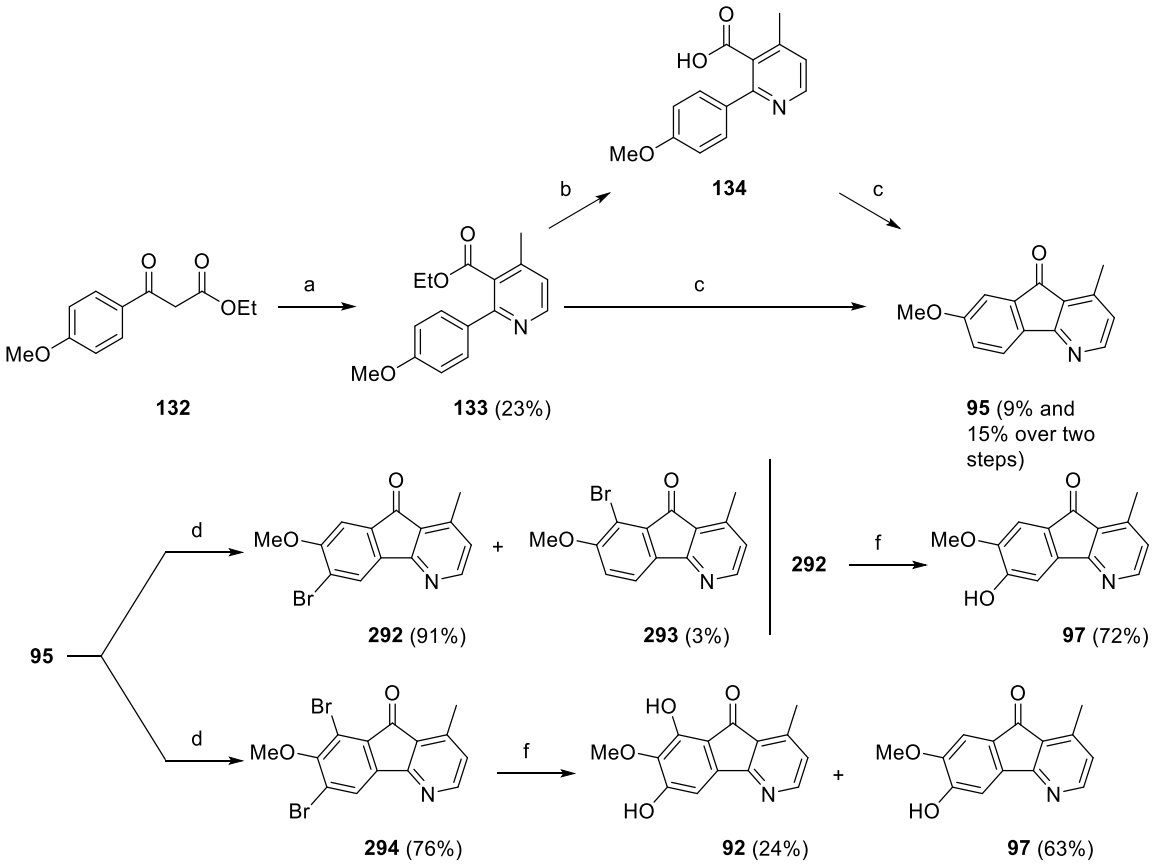
Reaction of 6-methoxyonychine (**91**) with two equivalents of NBS gave the desired product, 5,7-dibromo-6-methoxyonychine (**291**) in 26% yield. Oddly, the demethylation reaction observed during employment of one equivalent of NBS was not observed during this reaction. As is common with electrophilic substitutions, monobromination most likely deactivates the azafluorenone and discourages further bromination, resulting in low yields of dibrominated products.[204] Conversion of the dibromide **291**, however, did not yield the desired product cyathocaline (**94**). Instead, only trace amounts of the mono-hydroxylated intermediate was detected *via* mass spectroscopic analysis of the crude reaction mixture. The bromide-to-phenol conversion is compatible with aryl halides substrates bearing a free phenolic hydroxy group[206], therefore with enough of the mono-hydroxylated intermediate, further reaction to cyathocaline (**94**) might be possible. Considering the poor overall yield up to this step, this strategy did not seem feasible to pursue. Thus, further attempts at the total synthesis of cyathocaline (**94**) were not made.

4.4.4 Total synthesis of 7-methoxyonychine, oncodine and 6,8-dihydroxy-7-methoxyonychine

In theory, the alkaloid 7-methoxyonychine (**95**) should be readily accessible in only two steps from commercially available β-ketoester **132** (Scheme 70). With a yield of only 10%, construction of the pyridine ring under the standard conditions gave significantly less desired product **133** than for other substrates compared to the usual yield range of 30-40%. The formation of several unidentified side-products was observed, which were not detected for reactions with other β-ketoesters. During subsequent cyclization with PPA, 7-methoxyonychine (**95**) was isolated in a low yield of 9% next to unconsumed starting material (12%).

The synthesis of 7-methoxyonychine (**95**) has been previously described by Pan and coworkers, who employed a similar synthetic route.[136] Hereby, nicotinate ester **133** was furnished from β-ketoester **132** in a modest yield of 32%. Pan's protocol employed NaH as the catalytic base instead of benzyltrimethylammonium hydroxide and the reaction mixture was stirred for 90 minutes rather than 30 minutes after addition of hydroxylammonium chloride. The authors also describe having attempted the PPA-mediated cyclization of the nicotinate ester **133**, only obtaining a very low yield (the exact yield was not specified). The nicotinate ester **133** was then hydrolyzed to the carboxylic acid **134** with a yield of 66% and subsequently converted to the acyl chloride. $AlCl_3$-mediated Friedel-Crafts acylation in chlorobenzene then reportedly gave 7-methoxyonychine (**95**) in a yield of 25% over two steps.

In an effort to increase the overall yield towards 7-methoxyonychine (**95**), the synthesis of nicotinate ester **133** was repeated with the conditions reported by Pan et al.[136], affording the product with an improved yield of 23%. Alkaline ester hydrolysis furnished the crude carboxylic acid **134**, which was then cyclized with PPA to give 7-methoxyonychine (**95**) with a yield of 15% over two steps. Different from Pan's synthesis, the carboxylic ester **134** was not converted to the acyl chloride. However, the overall yield from ester **133** to 7-methoxyonychine (**95**) only differs marginally between the two methods (16.5% and 15%).



Scheme 70: Synthesis of 7-methoxyonychine (**95**) oncodine (**97**) and 6,8-dihydroxy-7-methoxyonychine (**92**).[90] Conditions: a) first NaH, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min; b) KOH, H_2O/EtOH (1:1), 100 °C, 16 h; c) PPA, 150 °C, 1.5 h; d) NBS (1.1 equiv.), conc. H_2SO_4, 50 °C, 1.5 h; e) NBS (2.1 equiv.), H_2SO_4 conc. 50 °C, 1.5 h; f) $Pd_2(dba)_3$, Me_4*t*BuXPhos, KOH, 1,4-dioxane/H_2O (1:1), 24 h, 100 °C. Total yield: 2.3% for **97** over five steps; 0.6% for **92** over five steps.

With 7-methoxyonychine (**95**) in hand, late-stage bromination was further explored. Monobromination led to a mixture of primarily 6-bromo-7-methoxyonychine (**292**) in 91% yield and a small amount of the 8-bromo derivative **293** in 3% yield. Conversion of 6-bromo-7-methoxyonychine (**292**) to the alkaloid oncodine (**97**) under standard conditions for the bromide-to-phenol conversion was accomplished in 72% yield.

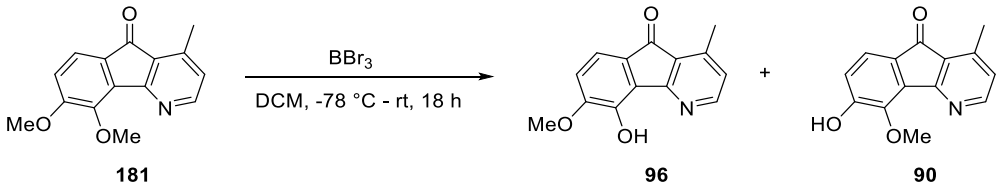
Bromide-to-phenol conversion of 8-bromo-7-methoxyonychine (**293**) would have led to the alkaloid macondine (**106**). However, the reaction gave too little of the required starting material **293** to continue the synthesis. Bearing in mind the unexpected reversal of regioselectivity towards bromination exhibited during synthesis of 5-bromo-6-hydroxyonychine (**289**, Section 4.4.3, Scheme 69), perhaps prior demethylation of 7-methoxyonychine (**95**) might facilitate regioselective bromination of C-8 and thus open a path towards macondine (**106**). This theory, however, was not put to the test.

Dibromination of 7-methoxyonychine (**95**) furnished 6,8-dibromo-7-methoxyonychine (**294**) in a yield of 76%. Subsequent bromide-to-phenol conversion, however, did not proceed as smoothly as usual. While the desired alkaloid 6,8-dihydroxy-7-methoxyonychine (**92**) was

afforded in a yield of 24%, the major product of the reaction was oncodine (**97**) with a yield of 63%. It seems that under standard bromide-to-phenol conversion conditions the conversion competes with the reductive removal of the bromide substituent. Formation of the other two possible reduction products 7-methoxyonychine (**95**) and macondine (**106**) was not observed. As is shown in later syntheses, susceptibility to reduction seems to be limited to bromide substituents at C-8 and arguably C-5. This marks the first total synthesis of 6,8-dihydroxy-7-methoxyonychine (**92**).

4.4.5 Total synthesis of isoursuline

Conversion of previously prepared 5,6-dimethoxyazafluorenone (**181**, Section 4.4.1, Scheme 60) to its monodemethylated derivatives, ursuline (**96**) and/or isoursuline (**90**) *via* Lewis acid promoted ether cleavage was also attempted (Scheme 71).

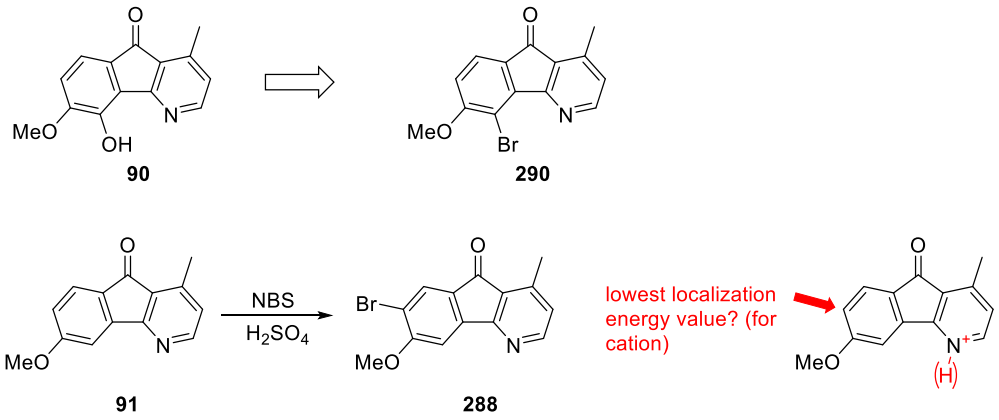


Scheme 71: Attempted synthesis of ursuline (**96**) and isoursuline (**90**) *via* *O*-demethylation of 5,6-dimethoxyazafluorenone (**181**).

Employment of equimolar amounts of the Lewis acid BBr_3 would ideally yield a mixture of both alkaloids in a close enough molar ratio that allows isolation of the two compounds. The reaction proceeded very sluggishly with most of the starting material unconsumed. What little starting material had reacted gave an inseparable mixture of both isomers with an apparent ratio of 1:4.73. However, it later became clear that isoursuline (**90**) partially decomposes during isolation by column chromatography on silica gel so that assessment of the isomeric ratio and the yield could not be determined accurately based on the isolated yields. A similar problem was described by Silveira et al. during their synthesis of 2-methyltriclisine, where demethylation of the intermediate 3,4-dimethoxyfluorenone with NaH and EtSH gave an inserparable mixture of both monodemetyhlated isomers.[177] The isomeric mixture was derivatized and successfully isolated in the next step by these authors. In the case of azafluorenone **181**, however, the sluggishness of demethylation necessitated addition of an excess of BBr_3. This approach ran risk of further demethylating the monomethyl derivatives, especially in presence of stabilizing electron-withdrawing groups *ortho*/*para* to the phenoxide intermediate.[208] Alternatively, a more suitable demethylation method had to be found. Furnishing enough substrate azafluorenone **181** to comfortably conduct such studies seemed unfeasible with the employed synthesis route, also bearing in mind that a suitable group for the subsequent derivatization and removal thereof had to be found. For this reason, this

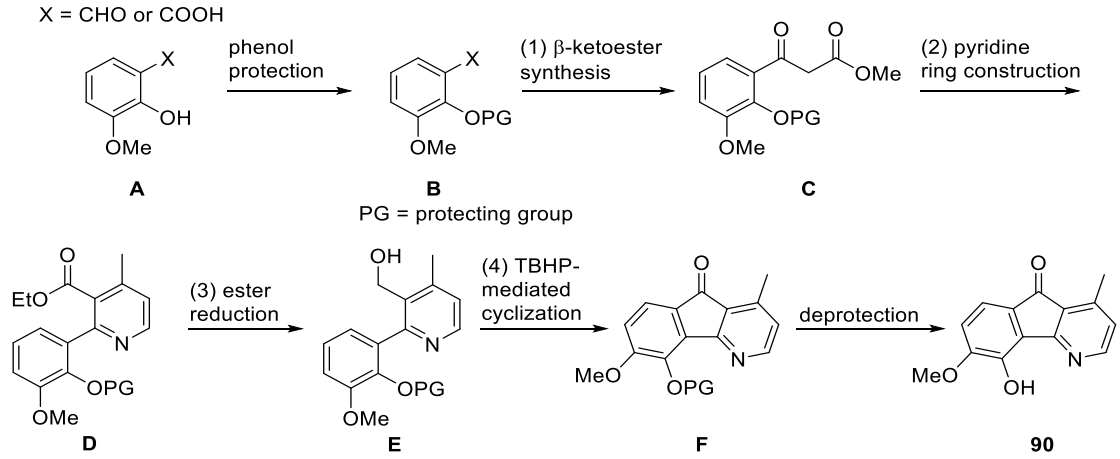
strategy was not explored any further, although it could have arguably also led to the desired results.

The problematic alkaloid from Bracher's Habilitation thesis, isoursuline (**90**, Section 4.4.1, Scheme 58), was therefore to be synthesized from scratch. Like darienine (**99**), and most other onychine-type alkaloids, isoursuline (**90**) bears a free phenol group. At the time this synthesis was planned and conducted, it seemed unlikely that bromination of the azafluorenone intermediate 6-methoxyonychine (**91**) would lead to the desired C-5 regioisomer **290** (Scheme 72). The L_r^+-values for unsubstituted 4-azafluorenone cation **282** suggest C-7 as the primary site of bromination. The directing effect of the C-6 methoxy substituent was unlikely to alter this pattern. With the chances of success being highly unlikely, different strategies were explored. In retrospective, it became evident that C-5 is indeed the preferred site of bromination for 6-methoxyonychine (**95**) following unexpected demethylation (Section 4.4.3, Scheme 69). However, late-stage functionalization would have still been less optimal due to the lower overall yield.



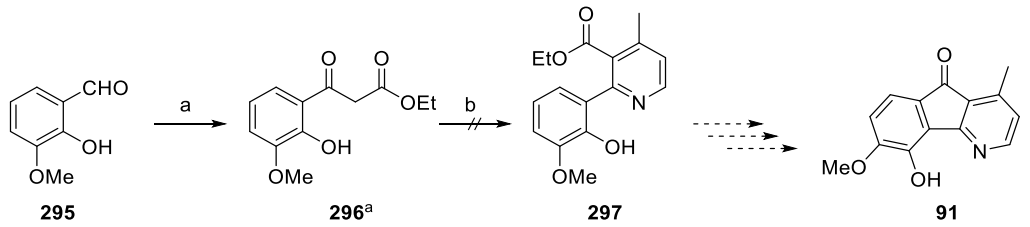
Scheme 72: Predicted outcome for the bromination of azafluorenone intermediate **91**.

Starting with commercially available benzaldehyde or benzoic acid **A**, the free phenol group would conceivably cause unwanted side reactions at some point during synthesis and necessitated protection thereof. A hypothetical phenol protecting group that was to be introduced during the first step of the total synthesis on starting material **A** would have to meet the following requirements: stability or chemical inertness against (1) mild Lewis acids ($SnCl_2$ or $MgCl_2$), (2) strong Brønsted bases (benzyltrimethylammonium hydroxide) and Brønsted acids at elevated temperatures (hydroxylammonium chloride, AcOH, 100 °C), (3) strong reducing agents (LAH) and (4) free radicals (Scheme 73).



Scheme 73: Considerations towards a phenol protecting group suitable for the synthesis of isoursuline (**90**).

Unfortunately, none of the more conventional protecting groups, for which stability charts are readily available, met all of the required conditions.[156] Therefore, a model synthesis with unprotected 2-hydroxy-3-methoxybenzaldehyde (**295**) was attempted to determine at which step the free phenol group would first undergo unwanted side reactions (Scheme 74). Depending on when protection of the free phenol group turned out necessary, stability of the protecting group against reaction conditions prior to this particular synthesis step would not be necessary, thus broadening the scope of suitable protecting groups. 2-Hydroxy-3-methoxybenzaldehyde (**295**) was also chosen to ascertain if phenolic hydroxy groups in *ortho*-position to the β-ketoester moiety would pose a unique challenge.



Scheme 74: Attempted model synthesis of isoursuline (**91**) with unprotected phenolic benzaldehyde **295**. Conditions: a) $SnCl_2$, EDA, DCM, rt, 1 h; b) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min. [a]inseparable mixture of starting material and product (keto and enol form).

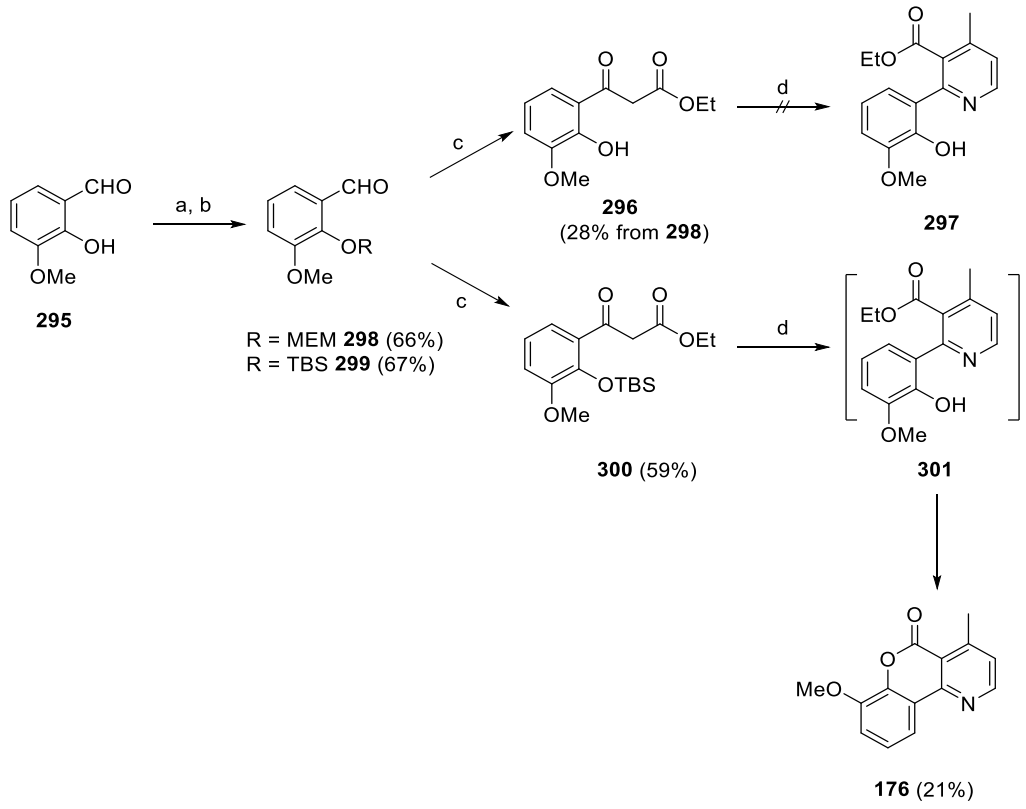
Reaction of 2-hydroxy-3-methoxybenzaldehyde (**295**) to the β-ketoester **296** gave an inseparable mixture of unreacted starting material and product identified *via* TLC-MS. Only a single direct conversion of this nature of a phenolic benzaldehyde to the corresponding β-ketoester has been described in the literature to date, in which the conversion of 4-hydroxybenzaldehyde with EDA and $NbCl_5$ is reported with a 60% yield.[209] It is therefore assumed that free phenolic groups should not interfere with the Lewis acid catalyzed addition of EDA to the aldehyde group. Based on earlier comparisons with the Roskamp method[198] (Section 4.4.1) and the fact that $NbCl_5$ and $SnCl_2$ serve the same function in the reaction mechanism, it was surmised that $SnCl_2$ used in this attempt should also yield similar results.

Reaction of the crude β-ketoester **296** to give the nicotinate ester **297**, however, gave multiple unidentified side-products. Formation of the desired product **297** was not observed *via* TLC-MS analysis of the crude reaction mixture. Of note, the unconsumed aldehyde **295** was the only substance that could be isolated in noteworthy amounts from the reaction mixture (31%). For similar reactions towards nicotinate esters with starting material containing unreacted aldehyde from the previous reaction, both aldehyde and β-ketoester are usually completely consumed.

It stands to reason that the free phenolic hydroxy group of 2-hydroxy-3-methoxybenzaldehyde (**295**) is prone to compete with the enolate ion as a Michael donor for reaction with crotonaldehyde. Phenols (pK_a ~10) being more acidic than β-ketoesters (pK_a ~11), means that the phenolic hydroxy group should be deprotonated primarily by the base benzyltrimethylammonium hydroxide in an approximate ratio of 10:1. Arguably, the pK_a values for both functional groups represent rough isolated estimates and are somewhat similar, but at the very least there is a competing acidic functional group for the base to deprotonate. The deprotonation step of β-ketoester **296**, bearing a free phenolic hydroxyl group, should therefore be inefficient. Employment of an excess of base, rather than catalytic amounts, did not yield better results. Moreover, the hydroxy group might react with reaction intermediates intramolecularly during the construction of the pyridine ring, due to the close spatial vicinity of the *ortho*-hydroxy group to newly formed moieties. For this reason, 2-hydroxy-3-methoxybenzaldehyde (**295**) may arguably not be the optimal model compound to explore the general viability of this synthesis route. However, even if nicotinate ester synthesis was successful with substrates bearing hydroxy groups in positions other than *ortho*, a unique solution for isoursuline (**90**) and other 5- and 8-oxygenated azafluorenone alkaloids would have still been needed. Synthesis of nicotinate esters with free phenolic hydroxy groups following the employed protocol have not been reported in the literature. However, Hantzsch dihydropyridines with hydroxyphenyl residues have been described, as an example of a reaction following a similar mechanism.[210]

Bearing in mind the original goal of this model synthesis, having only removed the first synthetic step from the equation, not enough criteria had been eliminated for there to be an obvious choice for a suitable phenol protecting group. Despite a low chance of success, this synthesis route was attempted with MEM- and TBS-protected starting materials **298** and **299**. The MEM-protected compound **298** was deprotected during β-ketoester synthesis, despite only catalytic amounts of Lewis acid $SnCl_2$ present, giving the unprotected compound **296**. Interestingly, the compound was furnished in a higher degree of purity than in the previous attempt at β-ketoester synthesis with unprotected compound **295**. Still, product formation was not observed during subsequent pyridine ring construction. Impurities present in the β-ketoester during the

previous attempt were therefore likely not what caused the reaction to fail. Conversely, β-ketoester synthesis worked surprisingly well with TBS-protected compound **299** despite the protecting group's bulkiness. Pyridine ring construction, however, afforded not the nicotinate ester **301** but the lactone **176**. Most likely, the unprotected nicotinate ester **301** is formed after acid induced TBS-cleavage but undergoes subsequent acid-induced lactonization with the liberated phenolic hydroxy group at elevated temperatures, showcasing the unsuitability of *ortho*-hydroxylated starting materials as previously discussed. It is however interesting to note that lactone formation was not observed for pyridine ring construction of the unprotected β-ketoester **296**, implying that the hydroxy group already interferes during enolate generation or Michael addition thereof to crotonaldehyde. Although no further efforts were made following this strategy in favor of developing a more unifying approach, it stands to reason that 6- and 7-hydroxylated azafluorenone alkaloids could be accessible *via* TBS-protected phenolic hydroxy groups, following reapplication of the protecting group, if need be, as previously done for the synthesis of the fluorenone-type natural product nobilone (**8**, Section 4.1.1, Scheme 34).

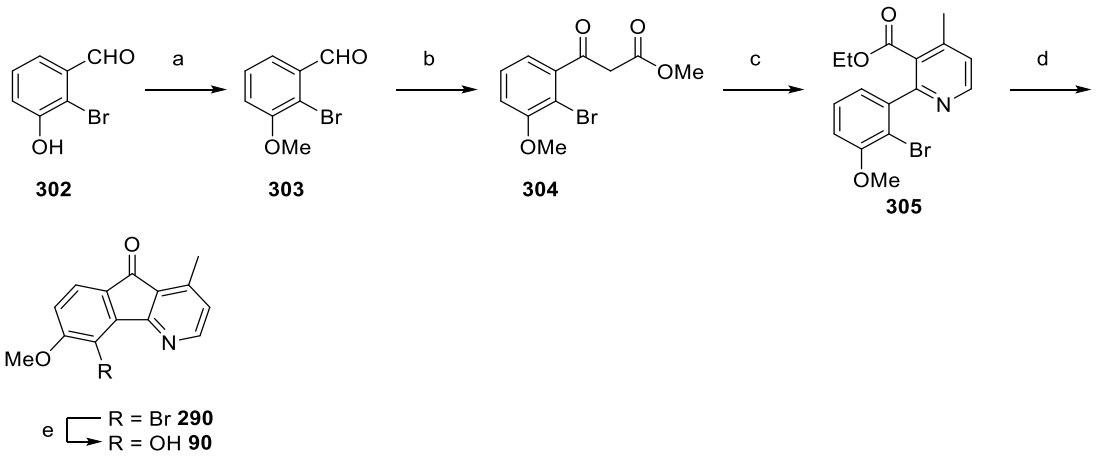


Scheme 75: Attempted model synthesis of isoursuline (**90**) with MEM- and TBS-protected phenolic benzaldehydes **298** and **299**. Conditions: a) MEMCl, NaH, DCM, rt, 19 h; b) TBSCl, imidazole, DMF, 50 °C, 18 h; c) $SnCl_2$, EDA, DCM, rt, 1 h; d) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min (yields given in parentheses).

Having exhausted options for phenol protection, the bromide-to-phenol conversion was revisited. Instead of introducing the latent hydroxy group *via* late stage-functionalization of

azafluorenones, either starting materials bearing bromide substituents at the appropriate positions available from chemical suppliers were used or bromide substitutents were introduced early on with brominating agents.

For the synthesis of isoursuline (**90**), commercially available 2-bromo-3-hydroxy-benzaldehyde (**302**) was *O*-methylated (Scheme 76). Preparation of the β-ketoester **304** was performed following Roskamp's method[198] with $SnCl_2$ and EDA and gave an inseparable mixture of starting material and product. The crude product **304** was reacted with crotonaldehyde and hydroxylammonium chloride to give nicotinate ester **305** in a yield of 18% over two steps. Cyclization with PPA furnished the desired brominated azafluorenone **290** in a yield of 21%.

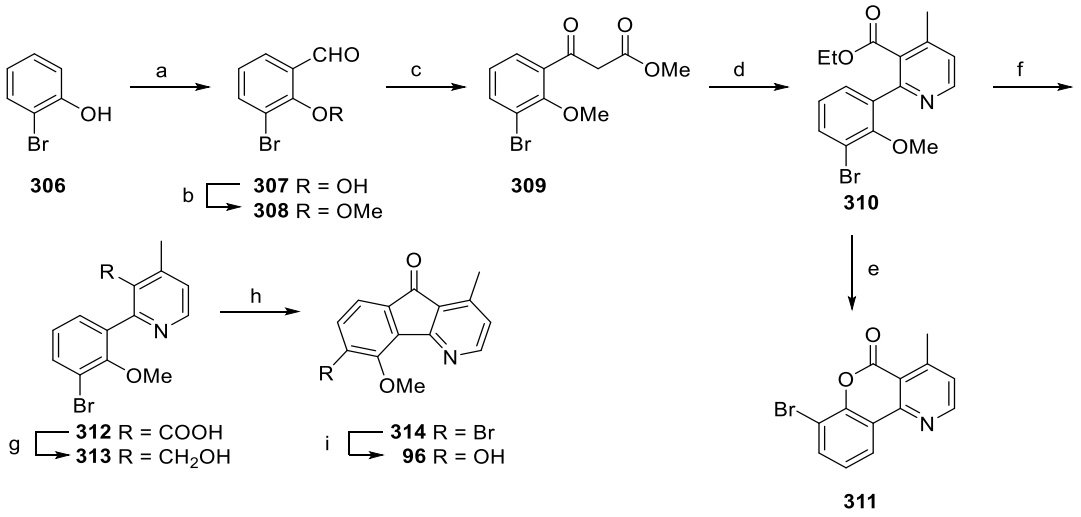


Scheme 76: Total synthesis of isoursuline (**90**). Reaction conditions: a) MeI, K_2CO_3, DMF, rt, 18 h, 98%; b) $SnCl_2$, EDA, DCM, rt, 1 h; c) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min, 18% over two steps; d) PPA, 140 °C, 1 h, 21%; e) $Pd_2(dba)_3$, Me_4*t*BuXPhos, KOH, 1,4-dioxane/H_2O (1:1), 18 h, 100 °C, 46%. Total yield: 1.7% over five steps.

It is possible to employ PPA for cyclization in this case because the bromide substituent acting as a placeholder obviates issues of lactonization. Finally, bromide-to-phenol conversion gave isoursuline (**90**) in 46% yield. Isolation of the natural product was conducted *via* preparative TLC as the compound proved largely unstable during column chromatography on silica gel. Arguably, a portion of the compound might have also decomposed on the preparative TLC plate (also lined with silica gel), reducing the yield of the final step to a certain degree. A different stationary phase might have been more suitable.

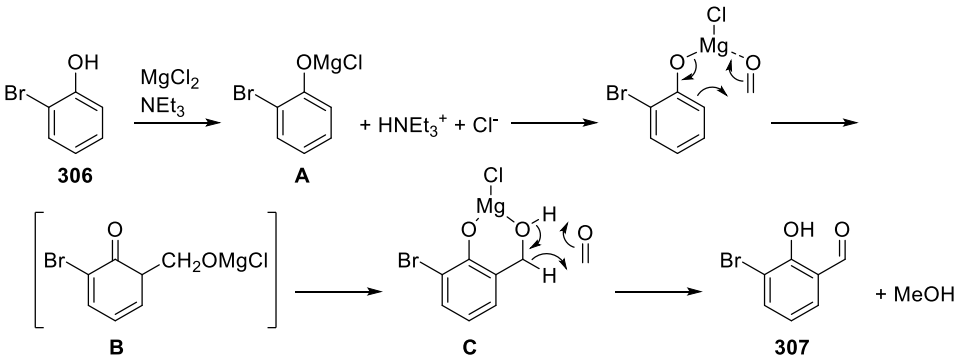
4.4.6 Total synthesis of ursuline

Next, the alkaloid ursuline (**96**) was synthesized (Scheme 77). To this end, commercially available 2-bromophenol (**306**) was *ortho*-selectively formylated[211] with formaldehyde, $MgCl_2$ and NEt_3.



Scheme 77: Total synthesis of ursuline (**96**). Reaction conditions: a) ethyl potassium malonate, $MgCl_2$, paraformaldehyde, NEt_3, THF, 100 °C, 18 h; b) K_2CO_3, CH_3I, DMF, rt, 16 h, 62% over two steps; c) $SnCl_2$, EDA, DCM, rt, 1 h, 35%; d) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min, 29%; e) PPA, 1.5 h, 150 °C, 62%; f) KOH, H_2O/EtOH (1:1), 100 °C, 4 h, 74%; g) $BH_3 \cdot SMe_2$, BMe_3, THF, 0 °C ⟶ rt, 39%; h) $TBHP_{non}$, 1,2-DCE, 100 °C, 18 h, 23%; i) $Pd_2(dba)_3$, Me_4*t*BuXPhos, KOH, 1,4-dioxane/H_2O (1:1), 18 h, 100 °C, 70%. Total yield: 0.3% yield over eight steps

A mechanism for this reaction proposed by the authors is shown in Scheme 78, exemplified with 2-bromophenol (**306**). Reaction with the $MgCl_2/NEt_3$ base system gives phenoxymagnesium chloride **A** (which could also be diphenoxymagnesium). Polymeric paraformaldehyde is cracked by heating to liberate monomeric formaldehyde. Magnesium further coordinates with the formaldeyde oxygen and brings it in close vicinity. The phenoxymagnesium is rearranged to cyclohexadienone structure **B** which gives the magnesium salt of salicyl alcohol **C** as the major product. Redox reaction of salicyl alcohol **C** with an additional molecule of formaldehyde gives salicyl aldehyde **307** and methanol.



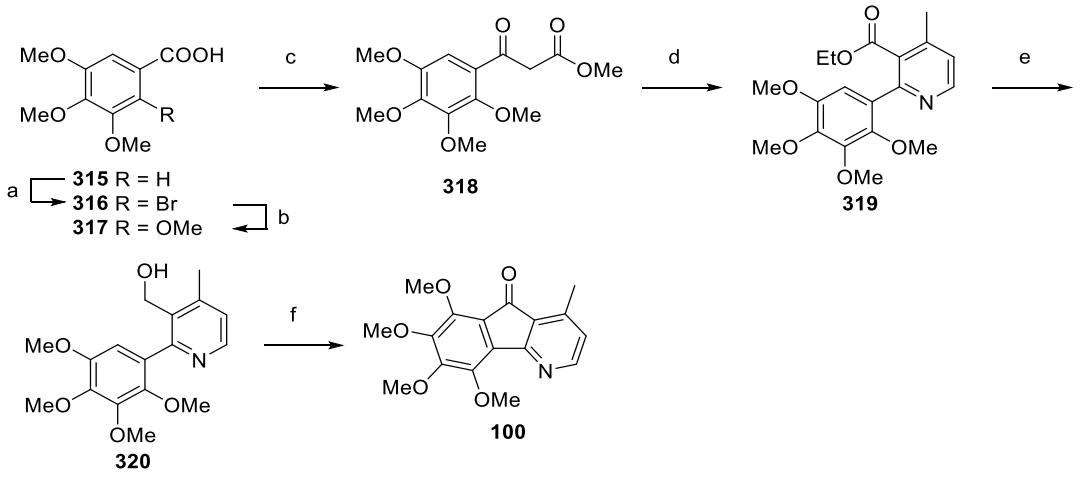
Scheme 78: Mechanism for the *ortho*-formylation of 2-bromophenol **306**.[211]

Following *O*-methylation of the crude aldehyde **307**, the methoxy derivative **308** was furnished in 62% yield over two steps. β-Ketoester **309** and nicotinate ester **310** were synthesized with 35% and 29% yield, respectively, employing the usual methods. As expected, PPA-mediated cyclization gave the lactone **311**, in a yield of 62%. Nicotinate ester **310** bears a methoxy substituent in *ortho*-position of the pyridine ring, so TBHP-mediated radical cyclization had to be employed to avoid lactone formation. For this purpose, nicotinate ester **310** had to first be reduced to the pyridinemethanol **313**. LAH is commonly employed for this conversion which, however, ran risk of also removing the bromide substituent.[212] In lack of any obvious alternatives that would allow for a convenient one-step reduction, the ester was first hydrolyzed under basic conditions in 74% yield to carboxylic acid **312**. Borane complexes chemoselectively reduce carboxylic acids in presence of a wide range of other functional groups susceptible to reducing agents, including halides.[213] During attempted reduction with borane-THF complex, however, no observable reaction took place and the starting material was recovered. Borane dimethylsulfide complex in presence of trimethyl borate gave the pyridinemethanol **313** in 39% yield. The borane dimethylsulfide complex has been reported to boast improved stability and solubility compared to the borane-tetrahydrofuran complex.[214] The exact mechanism of reduction of carboxylic acids with borane is unknown. The first step most likely involves formation of unstable triacylborates which activates their carbonyl oxygen's Lewis basicity towards borane. Addition of trimethyl borate was observed to increase the rate of reduction, likely by a similar activation.[215] In a blog post, a mechanism involving multiple cyclic transition states has been proposed by Emeritus Professor of Computational Chemistry at the Imperial College London, Henry Stephen Rzepa.[216] Finally, TBHP-mediated cyclization of pyridinemethanol **313** gave bromoazafluorenone **314** in a yield of 23%, which was subsequently converted under Pd-catalysis to the alkaloid ursuline (**96**) in 70% yield.

4.4.7 Total synthesis of 5,6,7,8-tetramethoxyonychine

For the synthesis of alkaloid 5,6,7,8-tetramethoxyonychine[94] (**100**), featuring a hexasubstituted benzene ring, carboxylic acid **315** was mono-brominated with NBS to give compound **316** (Scheme 79). Conversion of the bromide substituent to a methoxy residue was attempted as described by Meyers and coworkers with sodium metal and copper metal in anhydrous methanol[217], however, the starting material did not seem to react. Employing copper(I) bromide[218] instead of copper metal, gave the desired product **317** in close to quantitative yield. The established route of β-ketoester synthesis, pyridine ring construction and LAH reduction gave the pyridinemethanol **320**. Noticeably, the subsequent TBHP-mediated cyclization proceeded very sluggishly. Even with 8.0 equivalents of TBHP, the starting material had not been completely consumed after 40 h. This is somewhat reminiscent of a previously detailed attempt at the TBHP-mediated cyclization towards fluorenone **249**

bearing four methoxy substituents, where the aldehyde substrate **248** did not react presumably due to it being too electron-rich (Section 4.2, Scheme 47). In contrast to aldehyde **248**, the ring nitrogen of pyridinemethanol **320** might lower the molecule's electron-density just enough to allow for TBHP-mediated cyclization, albeit in a sluggish fashion. Addition of TBAI in a separate attempt facilitated the formation of multiple side-products not observed for other TBHP-mediated reactions, including a substance with the mass of the corresponding *tert*-butyl ester as determined by TLC-MS analysis. Ultimately, alkaloid 5,6,7,8-tetramethoxyonychine (**100**) was furnished in a yield of 14%.

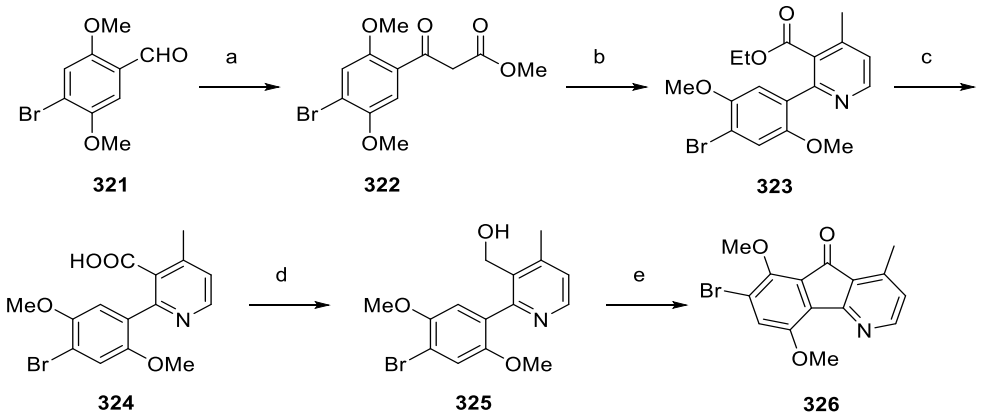


Scheme 79: Total synthesis of 5,6,7,8-tetramethoxyonychine (**100**). Reaction conditions: a) NBS, MeCN, rt, 16 h, 70%; b) Na, MeOH, CuBr, 70 °C, 18 h, 97%; c) first ethyl potassium malonate, $MgCl_2$, NEt_3, EtOAc, 0 °C → 35 °C, 6 h, then RCOCl derived from **317** ($SOCl_2$, 2 h, reflux), 0 °C → rt, 18 h, 54%; d) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min, 24%; e) LAH, THF, 18 h, 66%; f) $TBHP_{non}$, 1,2-DCE, 100 °C, 40 h, 14%. Total yield: 0.8% over six steps.

A total synthesis of alkaloid **100** has not been previously published.

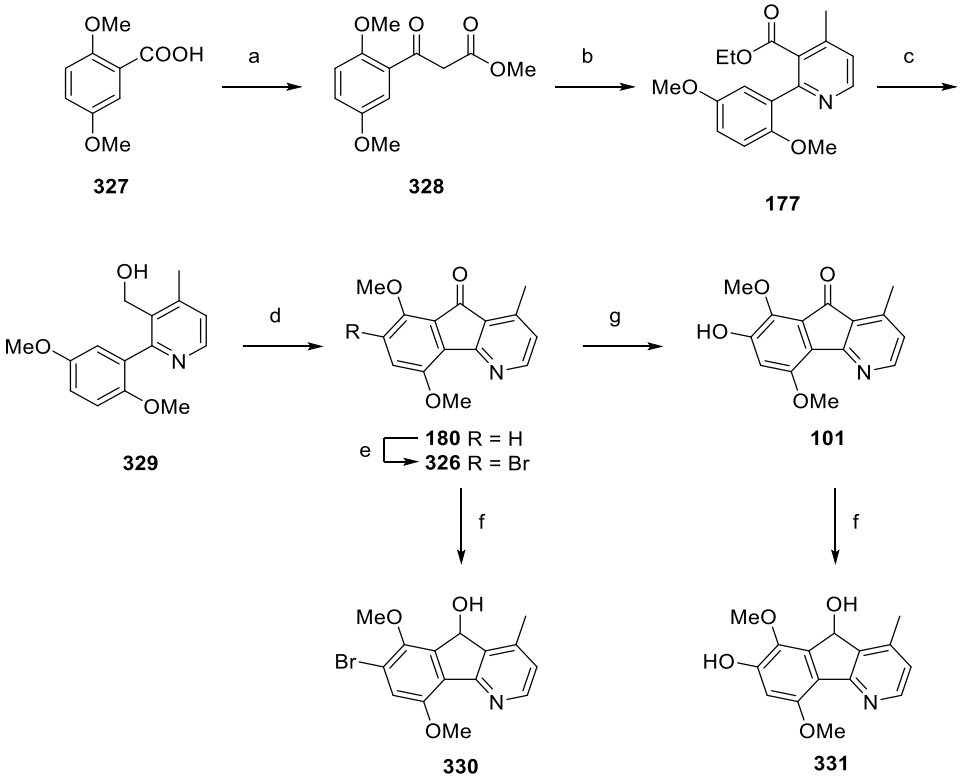
4.4.8 Total synthesis of 7-hydroxy-5,8-dimethoxyonychine

For the synthesis of alkaloid 7-hydroxy-5,8-dimethoxyonychine[95] (**101**), 4-bromo-2,5-dimethoxybenzaldehyde (**321**) available from chemical suppliers was reacted to give β-ketoester **322** with $SnCl_2$ and EDA (Scheme 80). Its isolation from side-products proved difficult so the crude β-ketoester **322** was then further reacted to nicotinate ester **323** in a yield of 16% over two steps. In the presence of the bromide substituent, the ester had to be reduced in two steps, as done previously for the total synthesis of ursuline (**96**, Section 4.4.6, Scheme 77), to the carboxylic acid **324** (66%) and then the pyridinemethanol **325** (21%), the latter of which proved challenging to purify. TBHP-mediated cyclization of the crude pyridinemethanol **325** gave the desired product **326** in a yield so low (6%), the synthesis had to be discontinued at this point.



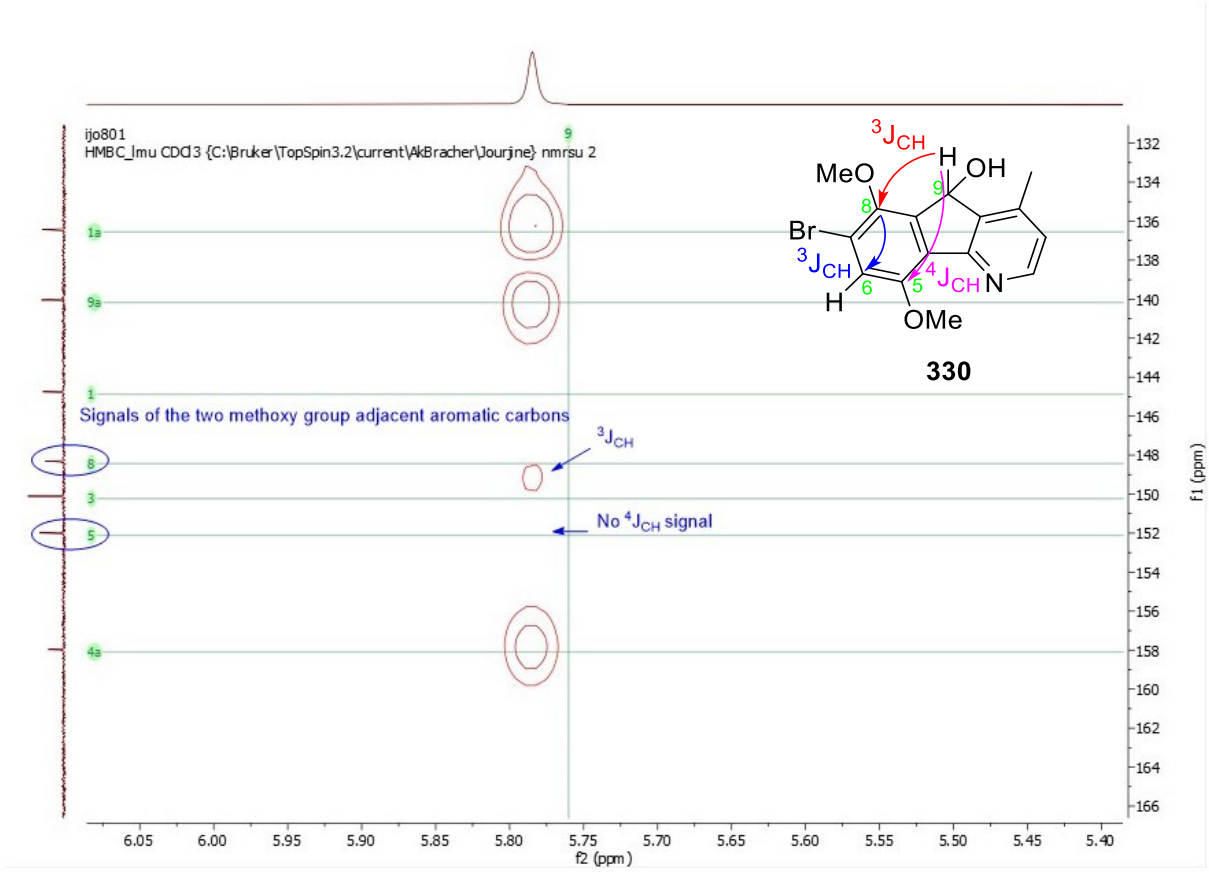
Scheme 80: Attempt at the total synthesis of 7-hydroxy-5,8-dimethoxyonychine (**101**). Conditions: a) $SnCl_2$, EDA, DCM, rt, 1 h; b) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min, 16% over two steps; c) KOH, MeOH, 80 °C, 16 h, 66%; d) $BH_3 \cdot SMe_2$, THF, 80 °C, 21% (crude yield); e) $TBHP_{non}$, 1,2-DCE, 100 °C, 18 h, 6%.

A second approach was then taken, wherein the latent phenolic hydroxyl group was to be introduced at a later stage of synthesis (Scheme 81). This had both advantages as well as disadvantages. Following the usual route, starting from commercially available 2,5-dimethoxybenzoic acid (**327**) to β-ketoester **328** and nicotinate ester **177**, a one-step reduction to pyridinemethanol **329** with LAH was conducted in absence of a bromide substituent.



Scheme 81: Synthesis of 7-hydroxy-5,8-dimethoxyonychine (**101**). Conditions: a) first ethyl potassium malonate, $MgCl_2$, NEt_3, EtOAc, 0 °C → 35 °C, 6 h, then RCOCl derived from **327** ($SOCl_2$, 2 h, reflux), 0 °C → rt, 18 h, 70%; b) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min, 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) $NaBH_4$, MeOH, rt, 1 h, 85% (for **330**), 91% (crude yield, for **331**); g) $Pd_2(dba)_3$, Me_4*t*BuXPhos, KOH, 1,4-dioxane/H_2O (1:1), 18 h, 100 °C, 59%. Total yield: 2.1% over six steps.

Subsequent TBHP-mediated cyclization gave 5,8-dimethoxyonychine (**180**) in a yield of 21%. The mono-bromination product **326** was furnished in high yields with NBS in H_2SO_4 and subsequently converted to the alkaloid **101**. However, it proved difficult to identify which of the two likely regioisomers had formed with NMR spectroscopy alone for both compound **326** and **101**. Structure elucidation solely based on the ^{13}C NMR chemical shifts for C-5 and C-8 was hereby deemed as too unreliable. Based on the L_r^+-values for the unsubstituted 4-azafluorenone cation **282**, it was to be expected that the 7-bromo derivative should form primarily during bromination of **180** (Section 4.4.2, Figure 7).[204] In case the 6-bromo derivative were to form, subsequent bromide-to-phenol conversion thereof would conveniently lead to another natural product for which no total synthesis has been previously reported called kinabaline (**102**).[74a] Azafluorenone **326** was furnished as an amorph solid, precluding X-ray crystallography. Therefore, the alkaloid **101** was to be reduced to the 4-azafluorenol **331** with $NaBH_4$ to facilitate structure elucidation *via* 2D NMR spectroscopy. Unfortunately, purification of the product turned out to be challenging due to the compound's high polarity. Instead, azafluorenone **326** was reduced to azafluorenol **330**, which proved easier to purify.



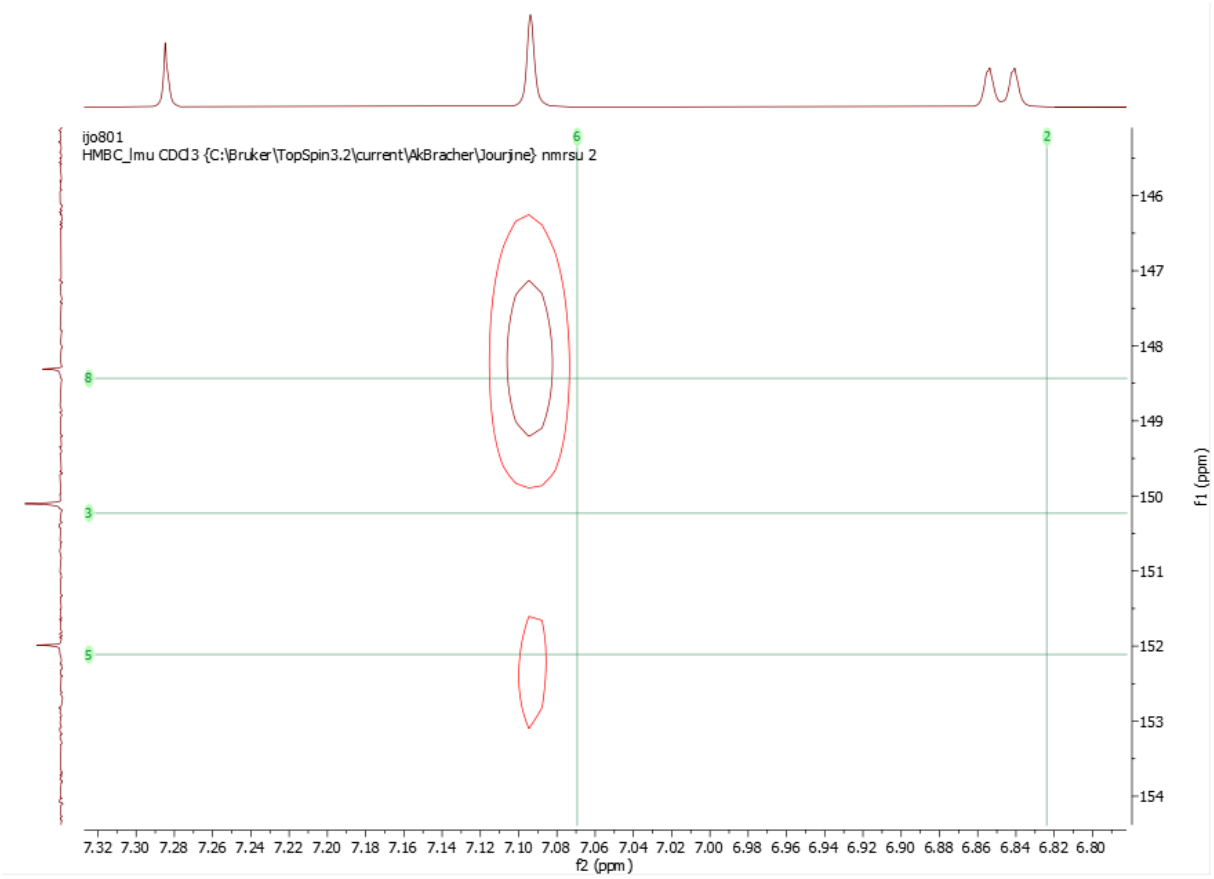


Figure 8: Structure elucidation of 4-azafluorenol **330** *via* Heteronuclear Multiple Quantum Correlation (HMBC) NMR experiment.

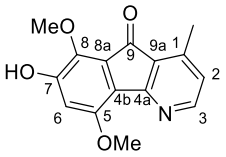
Distinction of the two aromatic carbons C-5 and C-8 bonded to methoxy groups was possible based on $^{3}J_{CH}$-coupling of 9-H to C-8 (Figure 8). Although the $^{3}J_{CH}$-coupling signal between the two nuclei was unexpectedly weak, $^{4}J_{CH}$-coupling signal of 9-H with the second methoxy group adjacent aromatic carbon was not measured as one would expect (first NMR spectrum, Figure 8). The carbon thus assigned as C-8 also shows a stronger coupling signal with the aromatic proton singlet in the HMBC spectrum than the second methoxy group adjacent aromatic carbon, meaning the singlet likely belongs to 6-H arising from $^{3}J_{CH}$-coupling, rather than 7-H arising from a weaker $^{2}J_{CH}$-coupling (second NMR spectrum, Figure 8). Lastly, the ^{1}H NMR chemical shifts of brominated 4-azafluorenone **326** obtained from the first synthesis attempt of 7-hydroxy-5,8-dimethoxyonychine (**101**) with commercially available starting material 4-bromo-2,5-dimethoxybenzaldehyde (**321**, Scheme 80), matched the ^{1}H NMR chemical shifts of brominated 4-azafluorenone **326** obtained from the second synthesis route exactly.

7-Hydroxy-5,8-dimethoxyonychine (**101**) is another alkaloid for which no total synthesis has been previously reported. The reported chemical shifts are compared with those measured with the synthetically prepared compound in Table 2.

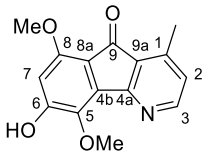
While some signals are relatively close in value, some of the more significant chemical shifts differ somewhat despite the NMR spectra for both compounds having been measured in the

same deuterated solvent, $CDCl_3$. Most notably, the chemical shift of 6-H for the compound isolated from *Unonopsis lindmanii*[95] was reported to be at 6.91 ppm, while the supposedly same proton was detected at 6.75 ppm for the synthesized compound. To rule out a possible misidentification with 7-hydroxy isomer kinabaline (**102**), the reported ^{1}H NMR data for this compound isolated from *Meiogyne virgata*[74a] is also shown in Table 2. The signal belonging to 7-H of kinabaline (**102**) reportedly lies at 6.34 ppm. Although the chemical shift of the singlet proton from the synthesized compound does not match the reported ppm-values for either isomer perfectly, it is closer in value to the chemical shift reported for 7-hydroxy-5,8-dimethoxyonychine (**101**). In combination with the spectroscopic data discussed earlier, the synthesized compound is most likely the 7-hydroxy regioisomer **101**.

Table 2: Comparison of ^{1}H and ^{13}C NMR chemical shifts of synthesized 7-hydroxy-5,8-dimethoxyonychine (**101**) with reported chemical shifts for the alkaloids **101** and **102** in the literature.



101



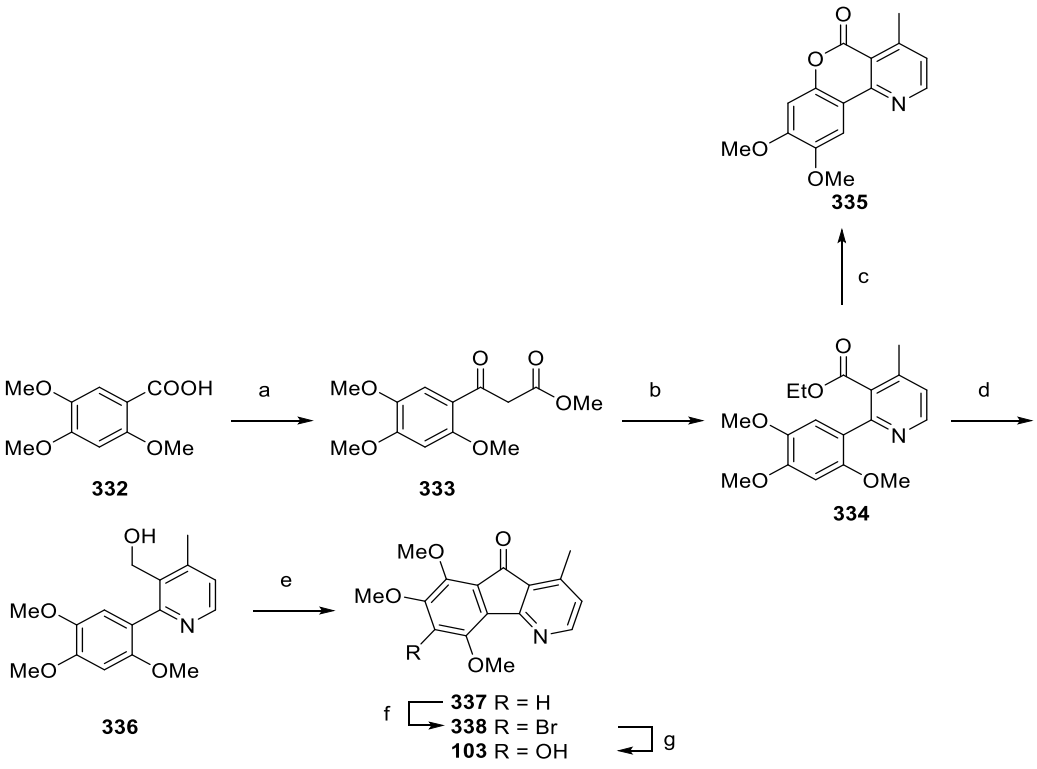
102

H	Chemical shifts (reported for **101**[95])[a]	Chemical shifts (reported for **102**[74a])[b]	Chemical shifts (synthesized)[c]	C	Chemical shifts (reported for **101**[95])[d]	Chemical shifts (reported for **102**[74a])[e]	Chemical shifts (synthesized)[f]
				1	149.2	n. r.[e]	147.3
2	6.86 (d, *J* = 5.2 Hz)	6.95 d (5.0)	6.81 (d, *J* = 5.3, 0.7 Hz)	2	124.6	n. r.[e]	124.0
3	8.23 (d, *J* = 5.2 Hz)	8.51 d (5.0)	8.42 (d, *J* = 5.2 Hz)	3	148.6	n. r.[e]	153.1
				4a	164.0	n. r.[e]	165.5
				4b	119.2	n. r.[e]	120.4
				5	156.4	n. r.[e]	152.5
6	6.91 (s)		6.75 (s)	6	101.5	n. r.[e]	105.5
7		6.34 (s)		7	147.2	n. r.[e]	153.2
				8	142.5	n. r.[e]	139.5
				8a	129.6	n. r.[e]	125.3
				9	190.7	n. r.[e]	191.2
				9a	126.0	n. r.[e]	125.9
1-CH_3	2.59 (s)	2.63 bs	2.59 (d, *J* = 0.7 Hz)	1-CH_3	17.3	n. r.[e]	17.5
5-OCH_3	3.92 (s)	3.93 s	3.98 (s)	5-OCH_3	56.5	n. r.[e]	56.7
7-OH	n.r.[g]	n.r.[g]	6.41 (bs)			n. r.[e]	
8-OCH_3	4.01 (s)	4.02 s	4.09 (s)	8-OCH_3	61.1	n. r.[e]	62.7

[a]$CDCl_3$, 300 MHz; [b]$CDCl_3$ 80.13 MHz; [c]$CDCl_3$, 400 MHz; [d]$CDCl_3$, 75 MHz; [e]not reported; [f]$CDCl_3$, 101 MHz.

4.4.9 Total synthesis of muniranine and polynemoraline C

For the synthesis of muniranine[96] (**103**) featuring a hexasubstituted benzene ring, 2,4,5-trimethoxybenzoic acid (**332**), available from chemical suppliers, was first converted to the β-ketoester **333** in 66% yield (Scheme 82). Subsequent reaction to the nicotinate ester **334** presented a unique challenge not observed for other nicotinate esters. In addition to the ester, several unidentified side products formed, which coeluted with the desired product in the most common solvent combinations. A small sample of pure product was isolated for analytical purposes *via* preparative TLC. From here, the crude nicotinate ester **334** was cyclized with PPA to give the lactone and natural product polynemoraline C[219] (**335**) in a yield of 4% over two steps. Like other PPA-mediated cyclizations performed as part of this thesis, the yield was very low and the presence of side-products from the previous reaction may have further reduced the yield. The crude nicotinate ester **334** was also reduced to the pyridinemethanol **336** with LAH, at which point isolation from the side-products of the previous step was possible, furnishing the product in a yield of 9% over two steps. The azafluorenone **337** was prepared *via* TBHP-mediated cyclization in 16% yield and bromination with NBS gave the next intermediate **338** in 65% yield.

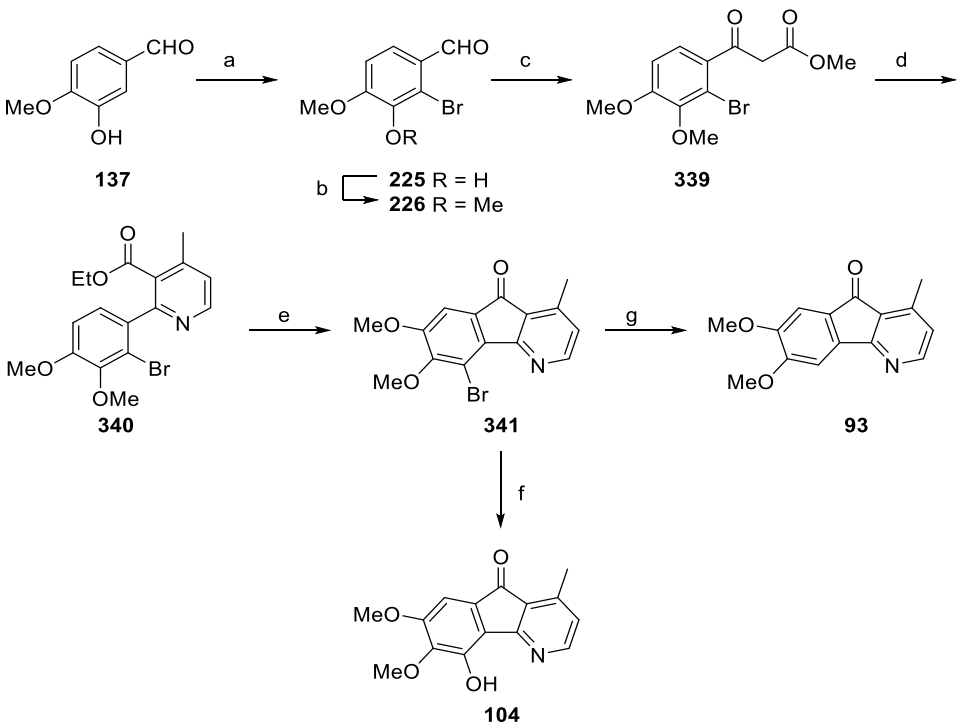


Scheme 82: Synthesis of polynemoraline C (**335**) and muniranine (**103**). Conditions: a) first ethyl potassium malonate, $MgCl_2$, NEt_3, EtOAc, 0 °C → 35 °C, 6 h, then RCOCl derived from **332** ($SOCl_2$, 2 h, reflux), 0 °C → rt, 18 h, 66%; b) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min; c) PPA, 1.5 h, 150 °C, 4% over two steps; d) LAH, THF, 18 h, 9% over two steps; e) $TBHP_{non}$, TBAI, 1,2-DCE, 100 °C, 18 h, 16%; f) NBS, H_2SO_4, 50 °C, 1.5 h, 65%; g) $Pd_2(dba)_3$, Me_4*t*BuXPhos, KOH, 1,4-dioxane/H_2O (1:1), 18 h, 100 °C, 63%. Total yield: 2.6% over three steps for **335**; 0.4% over six steps for **103**.

Finally, the natural product muniranine (**103**) was furnished following bromide-to-phenol conversion. Despite steric hindrance of two adjacent methoxy groups to the bromide substituent, the reaction employing the bulky Me$_4$*t*BuXPhos ligand was achieved with a good yield of 63%. Like isoursuline (**90**), the compound was observed to be somewhat unstable on silica gel. Isolation was therefore carried out *via* preparative TLC, minimizing exposure to silica gel. Muniranine has not been previously synthesized according to the literature.

4.4.10 Total synthesis of polyfothine and attempt at the total synthesis of 5-hydroxy-6,7-dimethoxyonychine

Finally, the two alkaloids polyfothine (**93**) and 5-hydroxy-6,7-dimethoxyonychine (**104**) were to be synthesized (Scheme 83). Starting from commercially available isovanillin (**137**), bromination with NBS in DCM as described by Aechtner and coworkers gave the desired product **225** as the sole regioisomer in nearly quantitative yield[178], as did subsequent *O*-methylation. The aldehyde **226** had already been prepared for the synthesis of 5,6-dimethoxyfluorenone (**229**) *via* this methodology (Section 4.2, Scheme 42). The aldehyde **226** was then converted to the β-ketoester **339** with $SnCl_2$ and EDA in 38% yield. Pyridine ring construction gave the nicotinate ester **340** in 31% yield and the azafluorenone **341** was furnished following PPA-mediated cyclization in 10% yield.

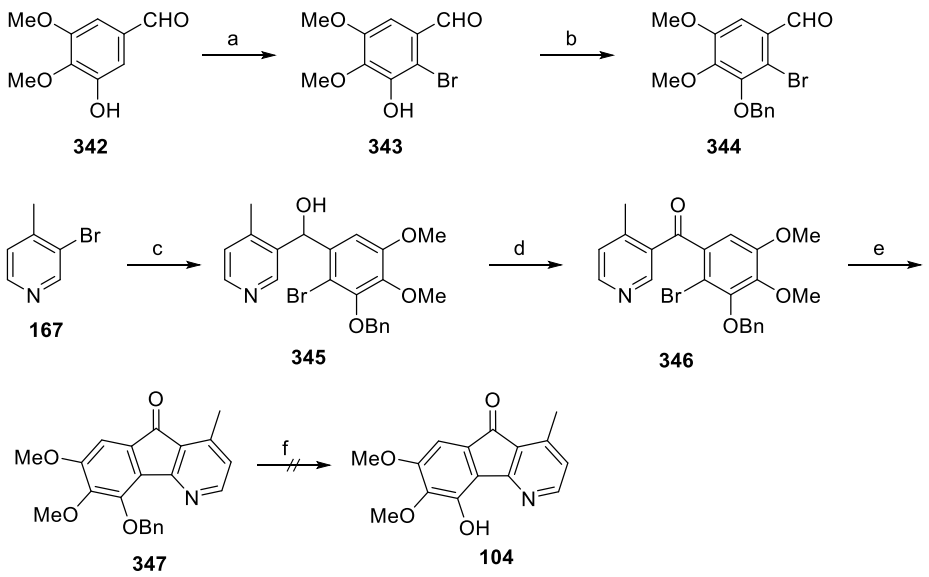


Scheme 83: Total synthesis of polyfothine (**93**) and attempted total synthesis of 5-hydroxy-6,7-dimethoxyonychine (**104**). Conditions: a) NBS, DCM, rt, 18 h, 95%; b) K_2CO_3, MeI, DMF, rt, 18 h, 96%; c) $SnCl_2$, EDA, DCM, rt, 1 h, 38%; d) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min, 31%; e) PPA, 140 °C, 1 h, 10%; f) $Pd_2(dba)_3$, Me$_4$*t*BuXPhos, KOH, 1,4-dioxane/H_2O (1:1), 18 h, 100 °C, trace amounts; g) B_2Pin_2, Pd(dppf)Cl_2 · CH_2Cl_2, KOAc, DMF, 80 °C, 18 h, 66%. Total yield: 0.7% over six steps.

This intermediate was envisaged to give access to two alkaloids. Reductive removal of the bromide substituent would lead to polyfothine (**93**), while bromide-to-phenol conversion would give 5-hydroxy-6,7-dimethoxyonychine (**104**). Reaction of azafluorenone **341** under the standard conditions for the bromide-to-phenol conversion unfortunately only gave trace amounts of the desired product **104** with most of the starting material not having been consumed. Lee and coworkers had previously reported the simultaneous conversion of two aryl bromide residues to the respective phenols in a two-step, one-pot reaction for the total synthesis of the resorcyclic acid lactone neocosmosin A.[220] Hereby, Miyaura borylation of the bromide residues afforded the bispinacolborane, which was subsequently oxidized with H_2O_2 under basic conditions to give the diphenol in a yield of 71% over two steps. Applying this protocol to bromoazafluorenone **341**, however, gave the debrominated starting material, which is an alkaloid itself called polyfothine (**93**), in an acceptable yield of 66%. Judging by TLC, most of the starting material had already been converted to polyfothine (**93**) prior to the oxidation step. It seems that the bromide residue at C-5 is susceptible to hydrodehalogenation.

A more deliberate attempt at the synthesis of polyfothine (**93**) was made with a Pd-catalyzed hydrodehalogenation with paraformaldehyde as the hydride source in DMSO.[221] This reaction did, however, not give the desired product **93**. Instead, it gave a mixture of unwanted side-products including a molecule with the mass of the bromofluorene, suggesting the carbonyl group had been reduced to the methylene group. The product mixture was not purified but only analyzed *via* TLC-MS. Reduction of aromatic halides is more commonly achieved *via* hydrogenolysis. In fact, the Bracher group previously achieved hydrodehalogenation of a bromide residue that was used to block a reactive site for PPA-mediated cyclization towards 8-methoxyonychine (**164**) with Raney nickel under an H_2-atmosphere discussed earlier (Section 1.2.2, Scheme 14).[199] Having exhausted the supply of starting material and, although by accident, having prepared polyfothine (**93**) in a step with sufficiently high yield, this reaction was not attempted.

Taking a different approach, the synthesis route employed for polyfothine (**93**) by the Kraus group[146] was applied in another attempt at the total synthesis of 5-hydroxy-6,7-dimethoxyonychine (**104**), with the starting material bearing a benzyl residue that was to be deprotected in the final step (Scheme 84).



Scheme 84: Second attempt at the total synthesis of 5-hydroxy-6,7-dimethoxyonychine (**104**). Conditions: a) NBS, THF, rt, 5.5 h, 99%; b) BnBr, K_2CO_3, DMF, rt, 18 h, 87%; c) *n*-BuLi, **344**, THF, -78 °C ⟶ rt, 18 h; d) MnO_2, DCM, rt, 40 h, 14% over two steps; e) TBAC, $Pd(OAc)_2$, K_2CO_3, DMF, 100 °C, 18 h, 7%; f) Pd/C, H_2, MeOH or AcOH, 22 h.

For the preparation of the aldehyde **344**, the *ortho*-directing effect of 2-hydroxy-3,4-dimethoxybenzaldehyde's (**342**) phenolic hydroxy group was exploited to furnish the desired product **344** upon bromination with NBS[222], followed by *O*-benzylation. In the next step, the *in situ* generated organolithium reagent derived from metal-halogen exchange of commercially available 3-bromo-4-picoline (**167**) and *n*-BuLi was reacted with aldehyde **344** to yield the secondary alcohol **345**. As described by the Kraus group, these alcoholic intermediates tend to be unstable. The crude alcohol **345** was therefore oxidized directly with MnO_2 in DCM. Unfortunately, the high yields reported for this method could not be replicated with starting material **344**. The first step in particular did not seem to proceed efficiently, as only small amounts of alcohol were detected *via* TLC next to multiple unidentified by-products. Another protocol[223] differing in the solvent employed, temperature and reaction time for the exact same type of reaction was also applied, however, no improvement regarding the amount of the desired alcohol formed was observed *via* TLC analysis. The amount of *n*-BuLi added was also subsequently increased in multiple attempts, and the rate of addition of aldehyde **344** was altered, however to no avail. Ultimately, the ketone **346** was furnished with a yield of 14% over two steps for the best attempt. Subsequent intramolecular Heck reaction with *tert*-butyl ammonium chloride (TBAC), $Pd(OAc)_2$ and K_2CO_3 gave a mixture of unreacted starting material, debrominated starting material, two unidentified side-products (possibly dimeric derivatives), and the desired product azafluorenone **347** in a poor yield of 7%. Judging by TLC, variations of this reaction with a different Pd-catalyst system ($Pd(OAc)_2$ and PPh_3, $Pd(PPh_3)_4$), ammonium salt (TBAI) or base (Ag_2CO_3) did not show any promising results. Debenzylation of azafluorenone **347** was then attempted *via* Pd-catalysed hydrogenolysis. No reaction was

observed with Pd/C under 1 bar of H_2 pressure after 18 h. The starting material **347** was reisolated and the more catalytically active[224] Pd black was used as the catalyst. Again, no reaction was observed after letting the mixture stir overnight under 1 bar of H_2 pressure. Finally, the reaction was carried out in acetic acid to suppress potential catalyst poisoning[225] by the ring nitrogen of substrate **347**. After 2 days, most of the starting material had not reacted, however, minor amounts of a new compound had formed. TLC-MS analysis of this compound suggested formation of the corresponding fluorenol with the benzyl group still intact. Other methods for clean removal of the benzylic ether in presence of methyl ethers could have been attempted. Yet, with less than 10 mg of crude starting material, no further attempts were made.

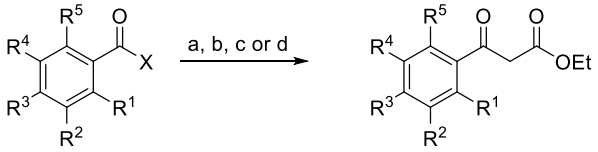
Partial results of this chapter were published in the European Journal of Organic Chemistry.[226]

4.5 Preparation of β-ketoester precursors – compilation of evidence gathered from diverse alkaloid total syntheses

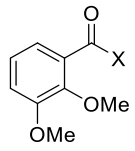
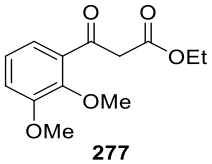
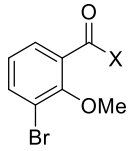
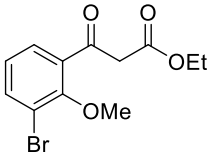
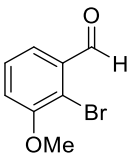
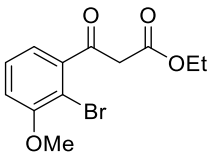
For the total synthesis of the natural product 6-methoxyonychine (**91**), Bracher successfully employed the method by Holmquist and Roskamp[198] to prepare the intermediate β-ketoester from benzaldehyde **160** in a yield of 66% (Section 1.2.2, Scheme 14).[199] Application of this method for the synthesis of other β-ketoesters as part of this thesis did not see the same success with yields ranging from 26% to 38% for those β-ketoesters obtained pure enough to determine their yield. This matches the general yields for aromatic aldehyde starting materials reported by Holmquist and Roskamp. The low projected total yields for the total syntheses attempted with this method necessitated starting material batch sizes of up to 25 g, which made purification *via* column chromatography challenging as both (unreacted) aldehyde, β-ketoester, and sometimes side-products, tend to have similar R_f-values and elute with wide bands/smears from the chromatography column. β-Ketoesters also give NMR spectra of varying complexity on account of two possible enol tautomers next to to the keto tautomer, further complicating discernment of the β-ketoester's degree of purity. On account of rather poor results, a few sporadic attempts at alternative methods for the preparation of β-ketoesters were made, such as using $NbCl_5$[201] as a Lewis acid substitute for $SnCl_2$. Carbethoxylation of the respective aryl methyl ketones with NaH and diethyl carbonate[227] was also endeavored. The products of some of these attempts were not isolated for determination of the respective yields, as comparison of TLC-plates gave results similar to the Roskamp method, and therefore deemed unnecessary. The few attempts with alternative methods of which the β-ketoesters were isolated from are listed in Table 3. Clay et al. reported a method for synthesis of β-ketoesters that also boasted high yields for aromatic substrates (benzoic acids and their chlorides) employing ethyl potassium malonate and the Mg-NEt_3 base system.[202] The comparatively high yields achieved with this method prompted a tabular comparison of the

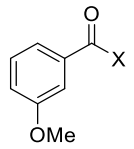
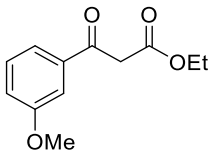
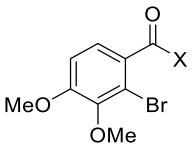
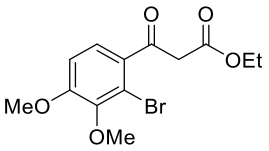
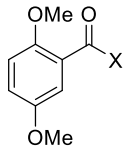
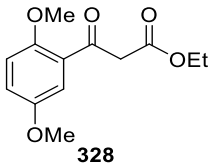
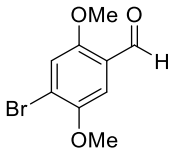
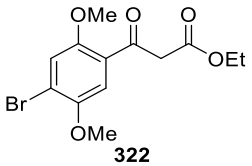
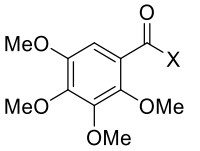
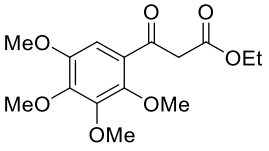
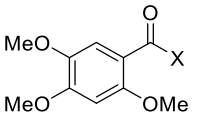
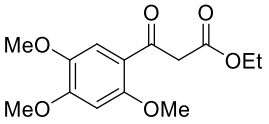
product yields for each method shown in Table 3. In case expensive starting materials had to be purchased (entry 3) or dead-end synthesis routes (entry 7), no comparison was attempted. This protocol was attempted only in the later stages of the azafluorenone project. Total synthesis for ursuline (**96**) had already been completed at this point in time. Therefore β-ketoester **309** was prepared on a small scale with Clay's method from benzoic acid **348** to avoid unnecessary waste of chemicals (entry 2). Even though a higher yield was achieved in comparison with Roskamp's method, the latter was depicted for the total synthesis (Section 4.4.6, Scheme 77) as the preparation of a large-scale batch might have resulted in a different yield. Clay's method furnished β-ketoester **309** in 51% yield but was conducted on a 2.83 mmol scale, while Roskamp's method gave β-ketoester **309** in 35% yield on an 84.3 mmol scale. Prepatations of β-ketoesters with Clay's method that are depicted for the total syntheses of 4-azafluorenone alkaloids have been conducted at the appropriate scale.

Table 3: Comparison between β-ketoester synthesis approaches. Conditions: a) $SnCl_2$, EDA, DCM, rt, 1 h; b) $NbCl_5$, EDA, DCM, rt, 1 h; c) NaH, diethyl carbonate, toluene, 110 °C; d) first ethyl potassium malonate, $MgCl_2$, NEt_3, EtOAc, 0 °C → 35 °C, 6 h, then RCOCl derived from carboxylic acid ($SOCl_2$, 2 h, reflux), 0 °C → rt, 18 h.



X = H, OH or CH_3
R = H, OMe or Br

Entry	Substrate	Product	Yield for method a[198]	Yield for method b[201]	Yield for method c[227]	Yield for method d[202]
1	 X = H **275** X = OH **276**	 **277**	38%	35%		67%
2	 X = H **308** or OH **348**	 **309**	35%			51%
3	 **303**	 **304**	n.d.*			

4	 X = OH **285** X = H **349** or Me **350**	 **286**	38%		n.d.*	82%
5	 X = H **226** X = Me **351** or OH **352**	 **339**	38%	n.d.*		36%
6	 X = H **353** or OH **327**	 **328**	n.d.*			70%
7	 **321**	 **322**	n.d.*			
8	 X = H **354** or OH **317**	 **318**	26%			54%
9	 X = H **355** or OH **332**	 **333**	n.d.*			66%

*Inseparable mixture of compounds containing the product eluted from the chromatography column for which the yield could not be determined.

It is worth mentioning that the method of Clay and coworkers[202] also seemed to be very sensitive to air and/or moisture. The synthesis of β-ketoester **333** was carried out multiple times with varying amounts of care given to providing an air and water free reaction environment (entry 9). For attempts done under air, yields were as low as 6% with most of the acyl chloride having hydrolyzed back to the carboxylic acid. The yield of 66% was reproducibly obtained in separate attempts when giving meticulous attention to excluding any potential sources of water from the reaction. Application of this protocol for the other substrates reported were therefore treated with the same caution. However, as syntheses of other β-ketoesters were performed only once for the most part, the possibility of trace amounts of water having lowered the yields

of some entries, in particular those with yields on the lower side like entry 5, cannot be ruled out.

4.6 Development of a GC-MS protocol for the identification of polycyclic aromatic alkaloids from Annonaceae

A GC-MS protocol for the identification of annonaceous polycyclic aromatic alkaloids was developed by Christoph Müller with assistance of Carolin Bauerschmidt based on a library of 25 relevant compounds compiled by the Bracher group over decades of total synthesis related research in this field. Fourteen of the compounds analyzed were prepared as part of this thesis including ten azafluorenone alkaloids, three unnatural congeners as well as polynemoraline C (**335**). The annonaceous alkaloids oncodine (**97**) and 7-methoxy-6,8-dihydroxyonychine (**92**) were prepared after publication of this study and were therefore not part of this investigation. The benzylisoquinolines annocherine A (**356**), annocherine B (**357**), *O*,*O*-dimethylannocherine A (**358**) originated from the PhD thesis of Benedikt Melzer. In addition, sampangine (**81**), eupolauridine (**82**), cleistopholine (**84**), lysicamine (**359**), eupolauridine mono-*N*-oxide (**360**), eupolauridine di-*N*-oxide (**361**), 3-methoxyonychine (**362**) and annomontine (**363**) as representatives of various annonaceous alkaloid classes were prepared by Franz Bracher decades ago.

The retention time of each compound was measured in relation to the internal standard (IS) fluorene, using a 5% phenyl polymethylsiloxane fused-silica capillary column as the stationary phase, based on which the temperature programmed Kováts retention index was determined.

$$I = 100 \times \left(\frac{t_{Ri} - t_{Rz}}{t_{R(z+1)} - t_{Rz}} + z \right)$$

I = Kováts retention index
t_{Ri} = total retention time of the substance
t_{Rz} = total retention time of the n-alkane
z = number of the carbon atoms of the n-alkane
$t_{R(z+1)}$ = total retention time of the n-alkane + 1 carbon atom

Equation 1: temperature programmed chromatography Kováts index equation as defined by IUPAC (International Union of Pure and Applied Chemistry).

The Kováts retention index is independent of analytical equipment and makes comparison of parameters obtained from different chromatographic systems possible. The Kováts retention index obtained for fluorene (1599 iu) closely resembled the average index listed in the NIST (National Institute of Standards and Technology) database of 1574 iu for 5% phenyl polymethylsiloxane capillary column, thus verifying the viability and feasibility of the method. The total ion chromatogram of all compounds is shown in Figure 9 and the Kováts retention indices determined for each analyte prepared as part of this thesis are shown in Table 4.

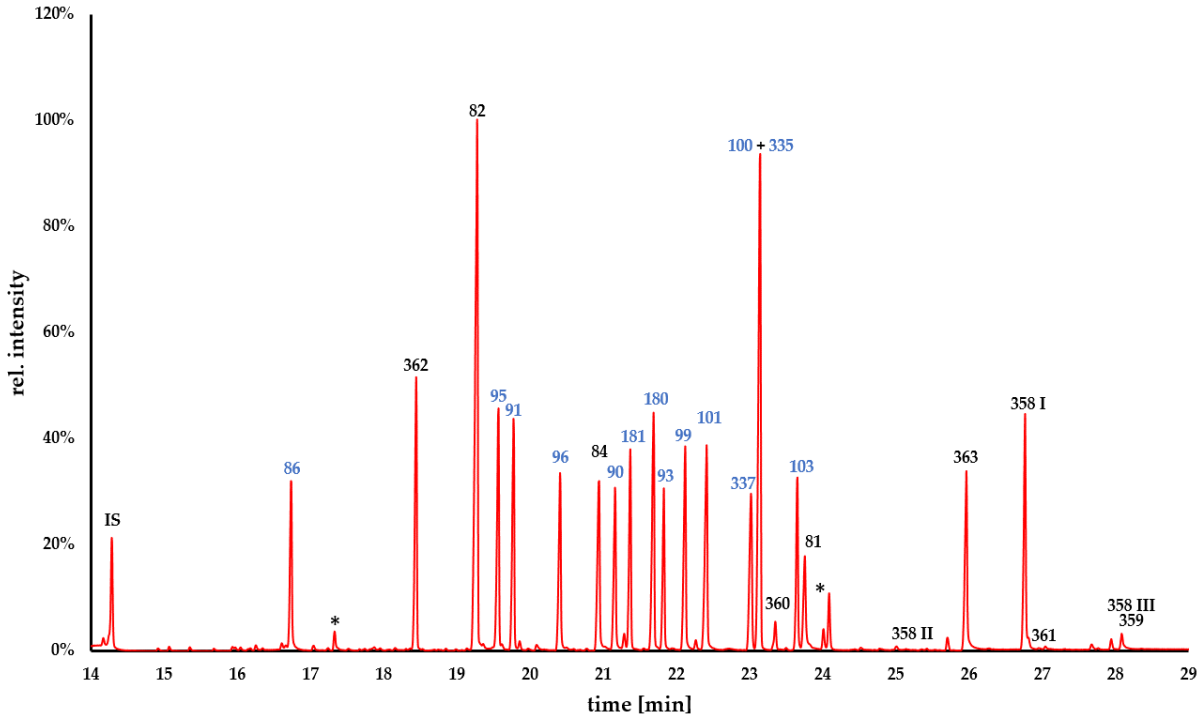
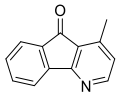
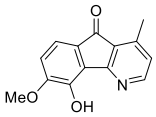
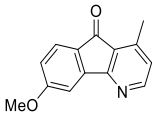
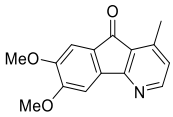
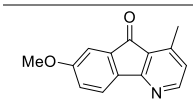
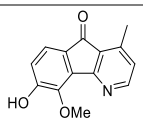
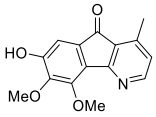
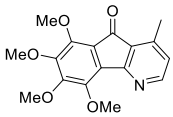
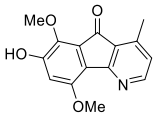
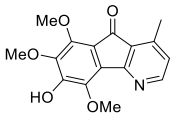
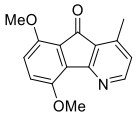
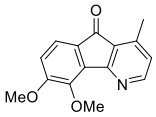
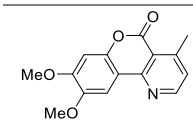
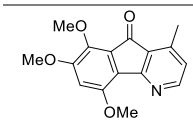


Figure 9: Total ion chromatogram of polycyclic aromatic alkaloids from Annonaceae (compounds prepared as part of this thesis are highlighted blue). Sampangine (**81**), eupolauridine (**82**), cleistopholine (**84**), onychine (**86**), isoursuline (**90**), 6-methoxyonychine (**91**), polyfothine (**93**), 7-methoxyonychine (**95**), ursuline (**96**), darienine (**99**), 5,6,7,8-tetramethoxyonychine (**100**), 7-hydroxy-5,8-dimethoxyonychine (**101**), muniranine (**103**), 5,8-dimethoxyonychine (**180**), 5,6-dimethoxyonychine (**181**), polynemoraline C (**335**), 5,7,8-trimethoxyonychine (**337**), *O*,*O*-dimethylannocherine A (**358**), lysicamine (**359**), eupolauridine mono-N-oxide (**360**), eupolauridine di-N-oxide (**361**), 3-methoxyonychine (**362**), annomontine (**363**); *impurities. Due to the individual volatility and thermal stability of the compounds, different concentrations were used in order to obtain a chromatogram visualizing the chromatographic behavior of all analytes (**81**, **82**, **84**, **86**, **90**, **91**, **93**, **95**, **96**, **99**–**101**, **103**, **180**, **181**, **335**, **337**, **359**, **363** and **IS** 20 μg/mL, **360** and **361** 50 μg/mL, **358** 100 μg/mL).

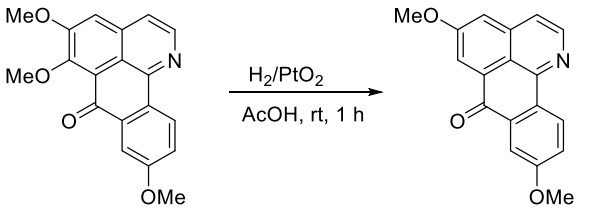
The Kováts retention index for onychine (**86**) listed in the NIST database is estimated to be 1772 iu, the experimental index lies at 1832 iu. No retention indices of other azafluorenones appear in the NIST database. The majority of analyzed azafluorenone compounds were easily separable and identifiable using a moderate heating rate of 10 °C/min. The sole exception were the alkaloids 5,6,7,8-tetramethoxyonychine (**100**) and polynemoraline C (**335**), which possess very similar RRT (1.621/1.617) and Kováts retention indices (2536 iu/2528 iu) using this method. A stationary phase with modified selectivity, like mid-polar columns with 50% phenyl 50% methylpolysiloxane, might allow for separation of both compounds. For information on compounds not prepared as part of this thesis, refer to the Molecules publication.[228]

Table 4. Azafluorenone alkaloids (and synthetic analogues) analyzed for the development of this protocol, including information on biological sources, chemical structure, MS data, and chromatographic properties.

Compound	Trivial name [biological source]	Chemical formula	M [g/mol]	Characteristic ions [*m/z*]	RRT (fluorene)	Kováts index
	Onychine[229] (86)	$C_{13}H_9NO$	195.07	**195**, 166, 139	1.171	1823
	Isoursuline[86] (90)	$C_{14}H_{11}NO_3$	241.07	241, **212**, 198	1.481	2290
	6-Methoxyonychine[230] (91)	$C_{14}H_{11}NO_2$	225.08	**225**, 182, 154	1.386	2135
	Polyfothine[79] (93)	$C_{15}H_{13}NO_3$	255.09	**255**, 212, 169	1.529	2371
	7-Methoxyonychine[92] (95)	$C_{14}H_{11}NO_2$	225.08	**255**, 210, 154	1.369	2108
	Ursuline[231] (96)	$C_{14}H_{11}NO_3$	241.07	**241**, 223, 183	1.430	2204
	Darienine[231] (99)	$C_{15}H_{13}NO_4$	271.08	271, **256**, 225	1.546	2400
	5,6,7,8-Tetramethoxyonychine[94] (100)	$C_{17}H_{17}NO_5$	315.11	**315**, 300, 239	1.621	2536
	7-Hydroxy-5,8-dimethoxyonychine[95] (101)	$C_{15}H_{13}NO_4$	271.08	**271**, 242, 172	1.566	2436
	Muniranine[232] (103)	$C_{16}H_{15}NO_5$	301.10	301, 283, **200**	1.653	2596
	5,8-Dimethoxyonychine (180)	$C_{15}H_{13}NO_3$	255.09	255, **254**, 226	1.516	2349
	5,6-Dimethoxyonychine (181)	$C_{15}H_{13}NO_3$	255.09	255, 254, **226**	1.494	2312
	Polynemoraline C[219] (335)	$C_{15}H_{13}NO_4$	271.09	**271**, 228, 185	1.617	2528
	5,7,8-Trimethoxyonychine (337)	$C_{16}H_{15}NO_4$	285.10	**285**, 270, 256	1.612	2519

4.7 Side project: Attempt at the total synthesis of bianfugecin

Bianfugecine (**183**) is an alkaloid of the class of oxoisoaporphines found in *Menispermum dauricum* DC and *Sinomenium acutum*.[233] Bianfugecine was found to be cytotoxic to human cancer cell lines A549, SK-MEL-2, XF498 and HCT15 with ED_{50} values ranging from 5.9 to 9.7 μg/mL.[233a] Tests with the cell lines SK-OV-3 showed a somewhat lower cytotoxicity with an ED_{50} value of 60.5 μg/mL. Further studies documenting its biological activity have not been reported in the literature thus far. A partial synthesis of bianfugecine (**183**) was first reported by Kunitomo and coworkers, where the alkaloid menisporphine (**365**) was converted to bianfugecine (**183**) in one step *via* catalytic demethoxylation over PtO_2 in acetic acid (Scheme 85).[234]

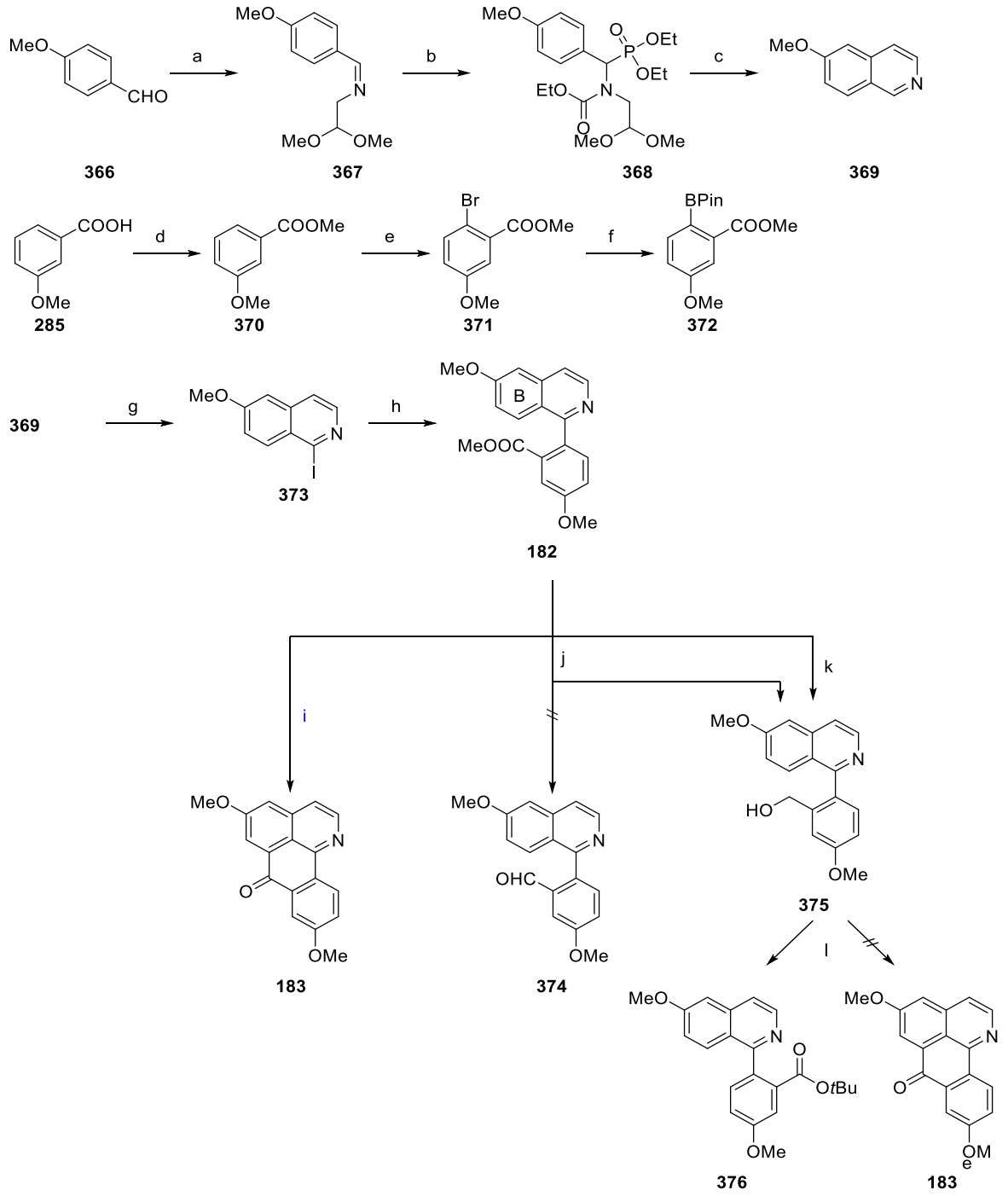


365 **183** (75%)

Scheme 85: Hydrogenolytic demethoxylation of menisporphine (**367**) to bianfugecine (**183**) over PtO_2.[234]

Benedikt C. Melzer, an alumnus of the Bracher group, worked out the first total synthesis of bianfugecine (**183**) as part of a novel approach to oxoisoaporphine alkaloids.[235] Cytotoxicity MTT tests with HL-60 cells, conducted as part of this thesis, measured an IC_{50}-value of > 50 μM.[150] No antimicrobial activity was detected against strains of *Escherichia coli*, *Pseudomonas marginalis*, *Streptococcus entericus*, *Yarrowia lipolytica*, *Candida glabrata*, *Aspergillus niger* and *Hyphopichia burtonii*.

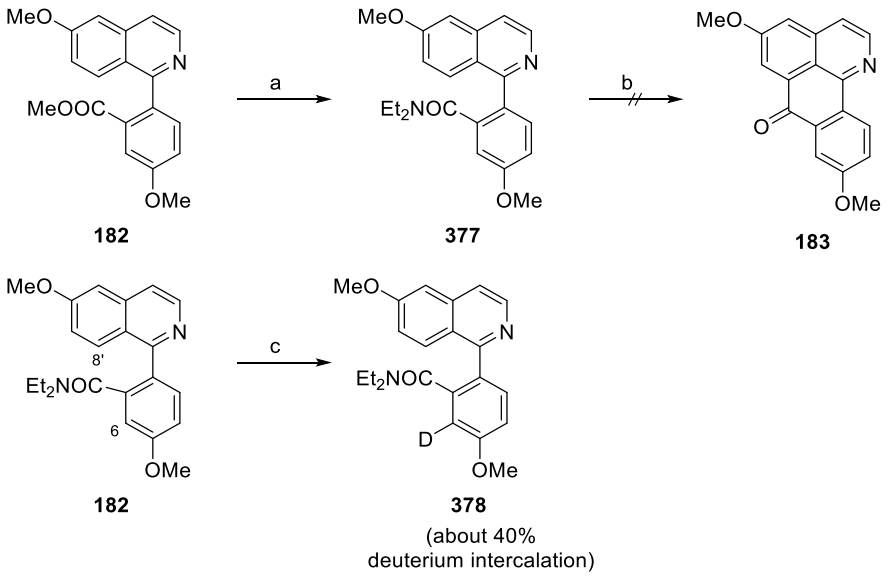
For its total synthesis, the building blocks isoquinoline **373** and pinacol boronic acid ester **372** were hereby prepared according to literature-known procedures (Scheme 86).[236]



Scheme 86: Total synthesis of bianfugecine (**183**) developed by Melzer.[235] Reaction i) was only performed by Melzer (highlighted in blue). The yields given for the other reactions were afforded through experiments performed by me following the synthesis route developed by Melzer. Conditions: a) aminoacetaldehyde dimethyl acetal, EtOH, reflux, 16 h; b) ethyl chloroformate, triethyl phosphite, THF, rt, 18 h; c) $TiCl_4$, DCM, reflux, 16 h, 45% over three steps; d) MeOH, conc. H_2SO_4, 100 °C, 18 h; e) NBS, PhSSPh, MeCN, rt, 16 h, 76% over two steps; f) B_2Pin_2, [(dppf)$PdCl_2$], KOAc, rt, 16 h, 71%; g) TMPMgCl LiCl, I_2, THF, rt, 5 h, 47%; h) **372**, $Pd(PPh_3)_4$, K_2CO_3, THF, 70 °C, 24 h, 41%; i) first conc. HCl_{aq}, 115 °C, 2.5 h; then Eaton's reagent, 90 °C, 2 h, 7%; j) DIBAL-H, DCM, -78 °C, 30 min; k) LAH, THF, rt, 18 h, 92%; l) $TBHP_{non}$, (TBAI), 1,2-DCE, 100 °C, 41 h, 8% (crude yield).

Reaction of 6-methoxyisoquinoline (**369**) with TMPMgCl·LiCl and subsequent quenching with iodine allows for regioselective iodination at C-1 and gave 1-iodo-6-methoxyisoquinoline (**373**). Suzuki cross-coupling with pinacol boronic acid ester **369** furnished the 1-arylisoquinoline **182**. From here multiple attempts at Friedel-Crafts-type ring closure methods towards bianfugecine

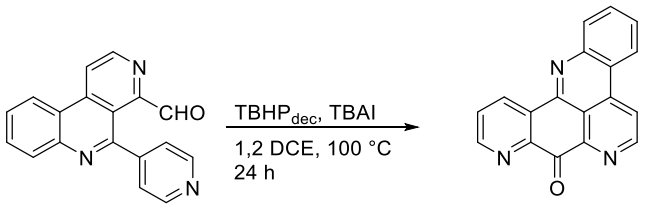
(**183**) in strongly acidic media were made by Melzer. These include 1) direct cyclization of ester **182** with triflic acid, acidic ester hydrolysis of **182** followed by 2) cyclization with triflic anhydride, 3) cyclization with Eaton's reagent (10 wt% P_4O_{10} solution in methanesulfonic acid) or 4) conversion to the acyl chloride and subsequent cyclization with $AlCl_3$. Only cyclization with Eaton's reagent after prior treatment with hydrochloric acid at 115 °C gave the desired product bianfugecine (**183**), albeit in a very low yield of 7%. It was hereby surmised, that ring B of the isoquinoline moiety of **182** was not sufficiently reactive for intramolecular Friedel-Crafts-type cyclization to proceed efficiently since cyclization of di- and trimethoxylated substrates worked well. Another approach was taken by Melzer for which the ester **182** was first converted to the diethylamide **377** (Scheme 87). Subsequent cyclization towards bianfugecine (**183**) was envisioned to be facilitated *via* directed remote metalation at C-8' of the isoquinoline ring with LDA. Unfortunately, this did not furnish the desired product. D_2O-„quenching"-experiments of the lithiated species showed that deuterium had intercalated exclusively at the C-6 position of the benzamide subunit rather than the desired C-8' position, preventing cyclization from occurring *via* the envisioned pathway (for more information and considerations on directed remote metalation refer to Benedikt Melzer's doctoral thesis).



Scheme 87: Directed metalation experiments toward the synthesis of bianfugecine (**183**) conducted by Benedikt Melzer.[150] Conditions: a) Me_3Al, Et_2NH, toluene, reflux, 2 h, 31%; b) LDA (4.0 equiv.) THF, 0 °C → rt, 3 h; a) first LDA (4.0 equiv.), THF, rt, 1 h; then D_2O

Having successfully employed the TBHP-mediated cyclization for ring closures inaccessible *via* Friedel-Crafts-type cyclizations in strongly acidic media previously, application of this methodology towards the synthesis of bianfugecine (**183**) was to be attempted in hopes of improving the yield of the cyclization step. To this end, ester **182** was prepared according to the synthesis developed by Melzer (Scheme 86). The ester **182** was then reduced to the benzyl alcohol **375** with LAH. Unexpectedly, subsequent treatment with TBHP, did not yield the

desired product, but instead a complex compound mixture. While the mass of bianfugecine (**183**), alongside the carboxylic acid, was identified from the crude reaction mixture, attempts at isolation of the main product of the reaction gave what is most likely the *tert*-butyl ester **376** with a crude yield of 8%, which coeluted with an inseparable side-product. Identification was hereby based on the mass spectrum and the clearly visible CH_3-signal of the *tert*-butyl group in the ^{1}H NMR spectrum. Formation of the *tert*-butyl ester has been previously observed for TBHP-mediated cyclization of pyridinemethanol **320** for the synthesis of the alkaloid 5,6,7,8-tetramethoxyonychine (**100**) upon addition of TBAI (Section 4.4.7, Scheme 79). A very similar undesired side-reaction was reported by Laha et al. during an attempt at TBHP-mediated cyclization of 4-(2-formylphenyl)pyridine, where the *tert*-butyl ester was furnished instead of the desired 2-azafluorenone.[133] This is the first attempt at the closure of a six-membered ring *via* TBHP-mediated cyclization, aside from unexpected formation of phenanthridine **1r** from amine **186r** (Section 4.1.3, Scheme 39), performed as part of this thesis. In 2021 the Wang group reported the synthesis of pyridoacridine alkaloids.[237] Therein, intramolecular acylation of formylated tricyclic benzonaphthydrine rings was, in some cases, performed with TBHP and catalytic amounts of TBAI (Scheme 88), which provided good yields.



379 **380** (66%)

Scheme 88: Example of TBHP-mediated six-membered ring closure for the total synthesis of pyridoacridine alkaloid demethyldeoxyamphimedine (**380**) reported by the Wang group.[237]

With this publication in mind, the TBHP-mediated cyclization of benzyl alcohol **375** was repeated according to the conditions employed by the Wang group (TBHP (2.5 equiv.), TBAI (10 mol%), 1,2-DCE, 100 °C, 24 h). However, the reaction again gave the same primary product *tert*-butyl ester **376**, the carboxylic acid and only trace amounts of bianfugecine (**183**) judging by TLC-MS and ASAP-analysis of the crude reaction mixture. Finally, the ester **182** was to be reduced to the aldehyde with diisobutyl aluminiumhydride (DIBAL-H) in DCM at -78 °C to closer recreate the Wang reaction conditions. DIBAL-H, as a reducing agent for the preparation of aldehydes from esters is notorious for its tendency towards overreduction, yielding significant quantities of primary alcohol.[238] Living up to its reputation, reaction of ester **182** gave the benzyl alcohol **375** as the sole product. Mild oxidation of the benzyl alcohol **375** could have potentially led to the desired aldehyde. However, no further attempts were made.

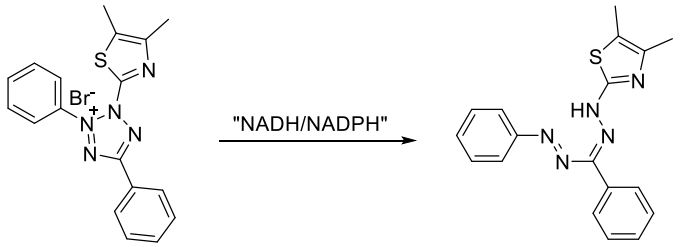
In summary, despite structural similarities between formylated tricyclic benzonaphthydrine educts employed by the Wang group[237] and the Melzer intermediates, none of the attempts at cyclization optimization with TBHP proved successful.

4.8 Biological testing

Routine testing for cytotoxicity *via* MTT assay and antimicrobial activity *via* agar diffusion assay of all 4-azafluorenone alkaloids prepared as part of this thesis were performed by Martina Stadler in the Bracher lab.

4.8.1 MTT-Assay

Prior to activity testing, the cytotoxicity of the prepared alkaloids were tested *via* colorimetric MTT assay, for which Mosmann's protocol was used (refer to Section 6.1 for details on the exact procedure).[239] The assay is based on the reduction of pale yellow tetrazolium salt MTT (**381**, 3-(4.5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) to dark blue formazan (**382**) when incubated with metabolically active cells (Scheme 89).



381 **382**

Scheme 89: *In vitro* reduction of MTT (**381**) to formazan (**382**).

The subcellular localization and the biochemical events involved in this process have been subject of much research but it most likely involves the pyridine nucleotide cofactors NADH and NADPH.[240] The amount of formazan (**382**) generated is proportional to the cell number as well as their activity. The absorbance of the colored formazan solution is measured photometrically and thus allows assessment of cytotoxicity and cell proliferation. For this assay, human leukemia cells (HL-60) were used. Triton X-100 served as the positive control. None of the compounds tested showed noticeable cytotoxic properties, as all IC_{50} values measured were greater than 50 μM.

4.8.2 Agar diffusion assay

The compounds were further screened for their ability to inhibit the growth of model bacteria (*Escherichia coli*, *Pseudomonas marginalis*, *Staphylococcus equorum*, *Streptococcus entericus*) and yeasts (*Yarrowia lipolytica*, *Saccharomyces cerevisiae*) *via* agar diffusion assay (refer to Section 6.1 for details on the exact procedure). Agar plates are inoculated with the

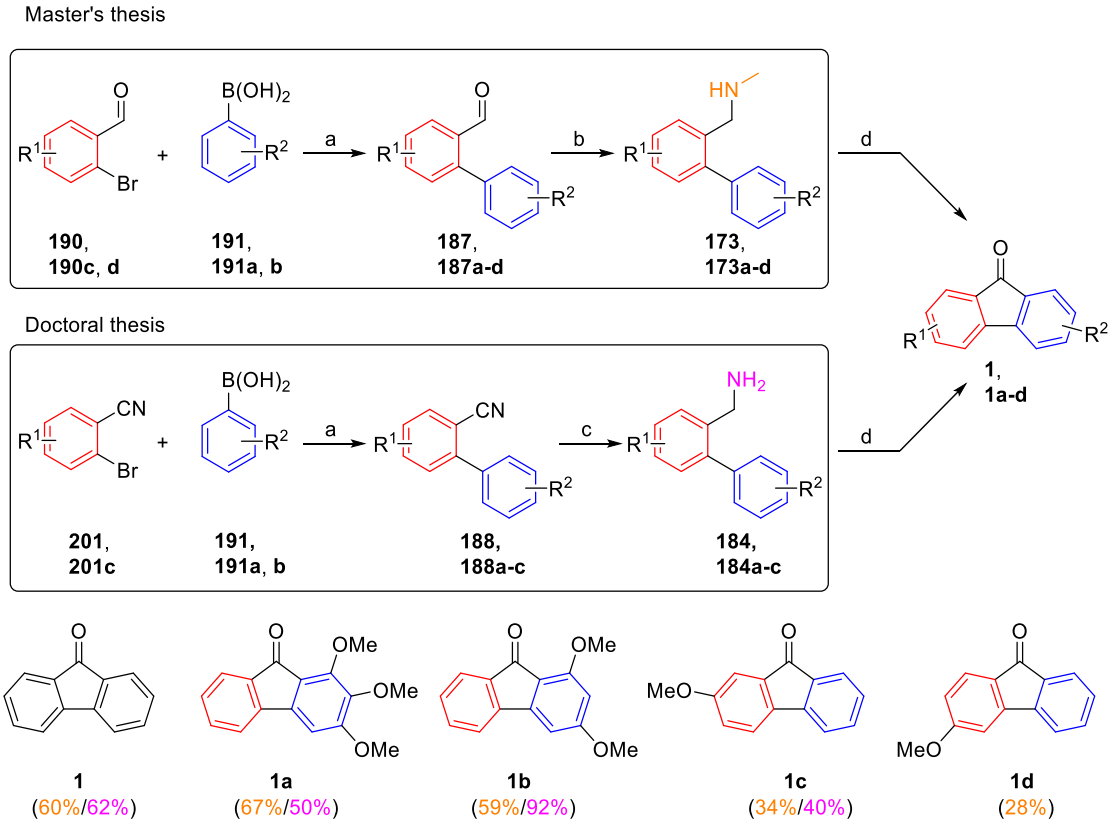
model microorganisms and diluted solutions of the compounds to be tested are applied to the surface. In case a compound exhibits antimicrobial activity, zones of growth inhibition appear on the agar plates, which differ in size depending on the compound's inhibition efficacy. As the diffusion characteristics of the respective compounds are not accounted for, this assay is purely qualitative. Tetracycline was used as a positive control reference for determination of antibacterial effects, and clotrimazole for determination of antimycotic effects. None of the compounds tested showed inhibition zones in the agar plates.

5 Summary

5.1 Synthesis of fluorenones

For the first main project, the research conducted during my Master's thesis was to be expanded upon. The *tert*-butyl hydroperoxide (TBHP)-mediated radical cyclization of *N*-methyl-2-(aminomethyl)biphenyls experimented with for the preparation of fluorenones **1** and **1a-d** was to be further optimized and characterized regarding its compatibility with commonly employed phenol protecting groups and different functional groups at the reaction center, as well as stereoelectronic effects of substituents.

The study began with an examination of 2-(aminomethyl)biphenyls **184** and **184a-c** as alternative substrates for the TBHP-mediated cyclization to the 2-(*N*-methylaminomethyl)biphenyls **173** and **173a-d** investigated during my Master's thesis (Scheme 90). In comparison with the *N*-methylamine substrates, the primary amines were also more readily accessible from a wider range of precursors such as nitriles.



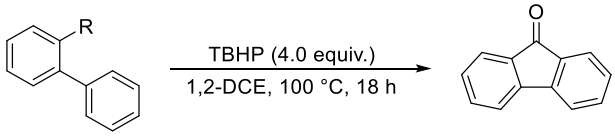
Scheme 90: Comparison of fluorenone synthesis approaches using 2-(aminomethyl)biphenyls and *N*-methyl-2-(aminomethyl)biphenyls as substrates for the TBHP-mediated radical cyclization. Conditions: a) $Pd(PPh_3)_4$, Na_2CO_3 or K_2CO_3, DMF/H_2O, 100 °C; b) $MeNH_2$, $NaBH_4$, DCM, rt; c) LAH, $AlCl_3$, THF, 0 °C ⟶ rt, 18 h; d) TBHP (aqueous or in *n*-decane), 1,2-DCE, 100 °C, 18 h (yields from both respective amine functional groups given in parentheses).

The primary amines **184** and **184a-c** were prepared in three steps starting from commercially available 2-bromobenzonitriles **201** and **201c** as well as phenylboronic acids **191**, **191a** and

191b, which were then reacted under Suzuki conditions to give the biphenyl-2-carbonitriles **188** and **188a-c**. Reduction with LAH/$AlCl_3$ and subsequent TBHP-mediated radical cyclization of the primary amines **184** and **184a-c** furnished the fluorenones **1** and **1a-c**. The yields differed somewhat from the *N*-methylamines **173** and **173a-c** for di- and trimethoxylated substrates while the yields for unsubstituted and monomethoxylated substrates were quite similar. Based on these results, both functional groups seemed compatible with the TBHP-mediated cyclization.

Other one-carbon functional groups were also tested for their affinity towards cyclization under the same conditions. A complete overview of related experiments conducted during my Master's thesis and the doctoral thesis is shown in Table 5.

Table 5: Reactivity of different functional groups towards TBHP-mediated cyclization to give fluorenone (**1**).



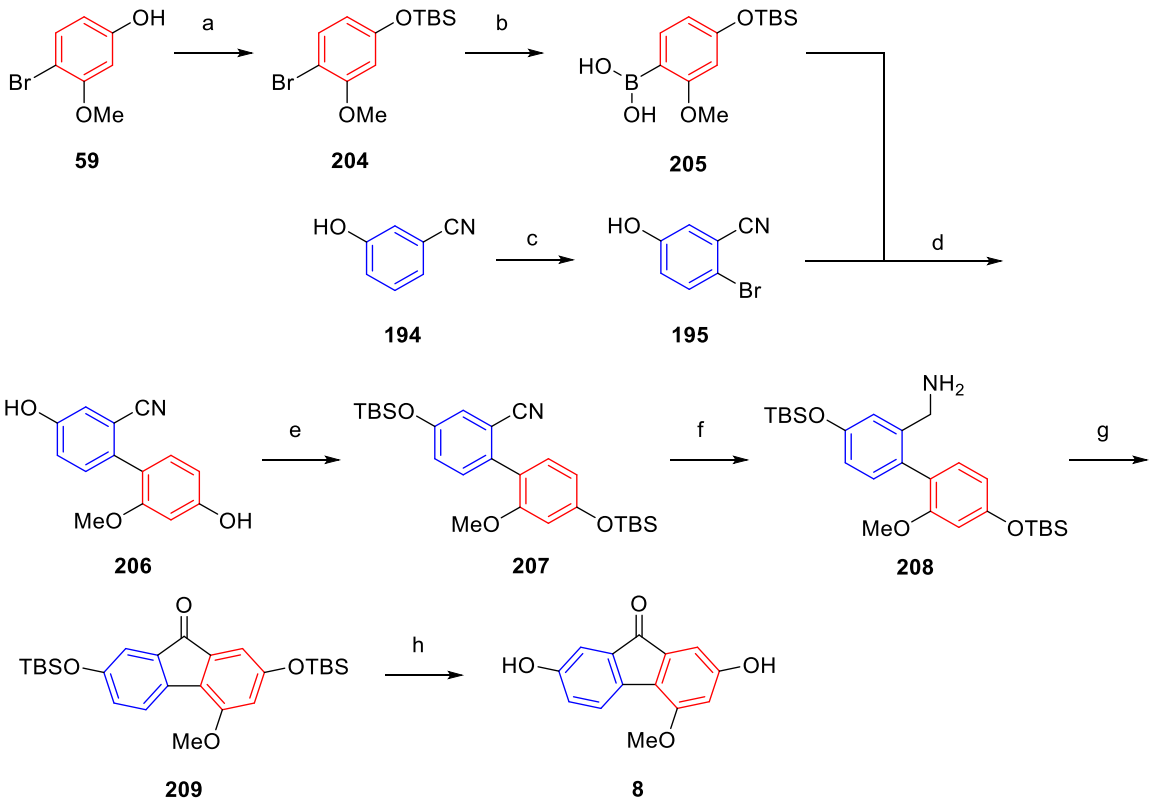
1

entry	R	Yield of **1**	entry	R	Yield of **1**	entry	R	Yield of **1**
1	CH_2NH_2	62[a] 22[b]	6	CH_2-morpholin-4-yl	[c]	11	CH_2OH	26[a] 60[b]
2	CH_2NHCH_3	60[a]	7	$CH_2NHCOCH_3$	[c] 20[a]	12	CHO	25[a] 26[b]
3	$CH_2N(CH_3)_2$	[c]	8	$CH_2NCH_3COCH_3$	0	13	CN	[c]
4	$CH_2NcC_4H_8$	[c] 13[a]	9	$CH_2NCH_3COCF_3$	[c]			
5	CH_2-pyrrolidon-1-yl	[c]	10	CH_2NCH_3Boc	[c]			

[a]isolated yields of the reactions carried out with aqueous TBHP (70%); [b]isolated yields of the reactions carried out with TBHP solution in *n*-decane (5.5 M); [c]Trace amounts or no product formation determined by TLC monitoring and GC–MS analysis as part of the initial screening.

Notably, the importance of which solvent TBHP is dissolved in became apparent. The primary amine **184** and the *N*-methylamine **173** performed poorly with TBHP dissolved in *n*-decane but gave good yields for fluorenone (**1**) with TBHP dissolved in water (entries 1 and 2) while the opposite behavior was observed for the benzyl alcohol precursor (entry 11). This suggested that water has a promoting effect for TBHP-mediated cyclization of benzylamines. For further studies, the primary amines were chosen over *N*-methylamines because the starting materials were more readily available.

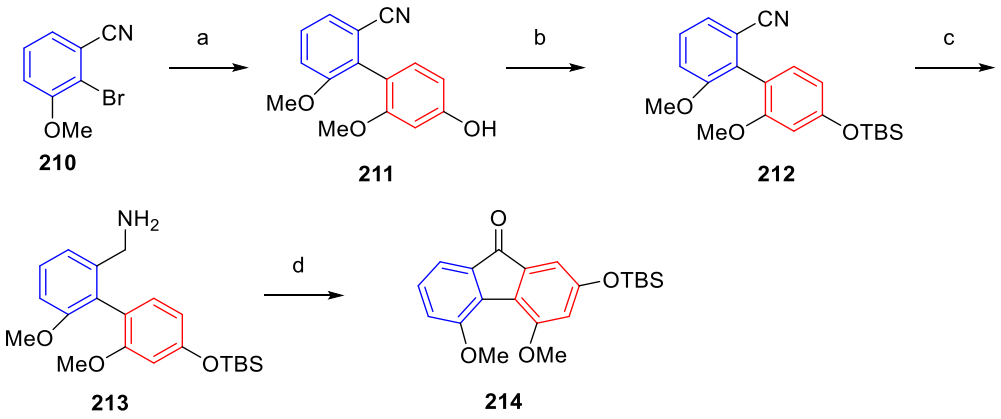
The developed method was to be used for the synthesis of fluorenone natural products which commonly bear free phenolic hydroxy groups. Poor results for TBHP-mediated cyclization of a 2-(aminomethyl)biphenyl substrate bearing a free hydroxyl group necessitated protection thereof. An initial attempt at the total synthesis of fluorenone alkaloid nobilone (**8**) with Bn-protected phenol groups was made but ultimately failed due to the incompatibility of benzyl ethers with the TBHP-mediated radical cyclization. A more suitable phenol protecting group for the TBHP-mediated cyclization was searched for through experiments with model compounds, during which the TBS group yielded the best results and total synthesis of nobilone (**8**) was reattempted (Scheme 91).



Scheme 91: Total synthesis of nobilone (**8**) with TBS protecting groups. Conditions: a) TBSCl, imidazole, DMF, 50 °C, 18 h, 97%; b) *n*-BuLi, $B(O^iPr)_3$, THF, -78 °C ⟶ rt, 16 h, 66%; c) $BF_3{\cdot}OEt_2$, NBS, MeCN, -20 °C ⟶ rt, 24 h, 51%; d) $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O (1:1), 100 °C, 12 h, 41%; e) TBSCl, imidazole, DMF, 50 °C, 18 h, 87%; f) LAH, $AlCl_3$, THF, 0 °C ⟶ rt, 12 h, 80%; g) $TBHP_{aq}$, 1,2-DCE, 100 °C, 18 h; h) hydrogen fluoride pyridine, methoxytrimethylsilane, EtOAc, rt, 4.5 h, 58% for two steps. Total yield: 5% over 8 steps.

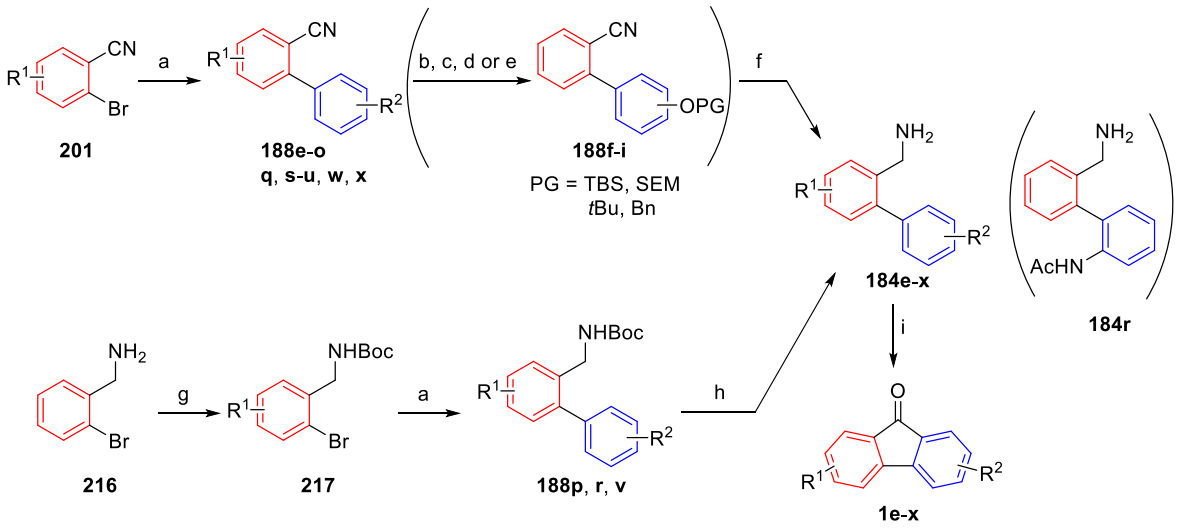
The TBS protecting group is susceptible to cleavage under basic conditions at elevated temperatures and should have ideally been introduced after Suzuki coupling. However, preparation of the phenylboronic acid building block **205** went more smoothly with the protected species and the TBS group had to be reintroduced following Suzuki coupling with bromobenzonitrile **195**. TBHP-mediated cyclization of benzyl amine **208** gave an inseparable mixture of fluorenone **209** and the aldehyde. Separation of both compounds was attempted following deprotection, but ultimately proved difficult and gave the alkaloid nobilone (**8**) in 58% yield with about 10% of remaining aldehyde impurity as determined by ^{1}H NMR.

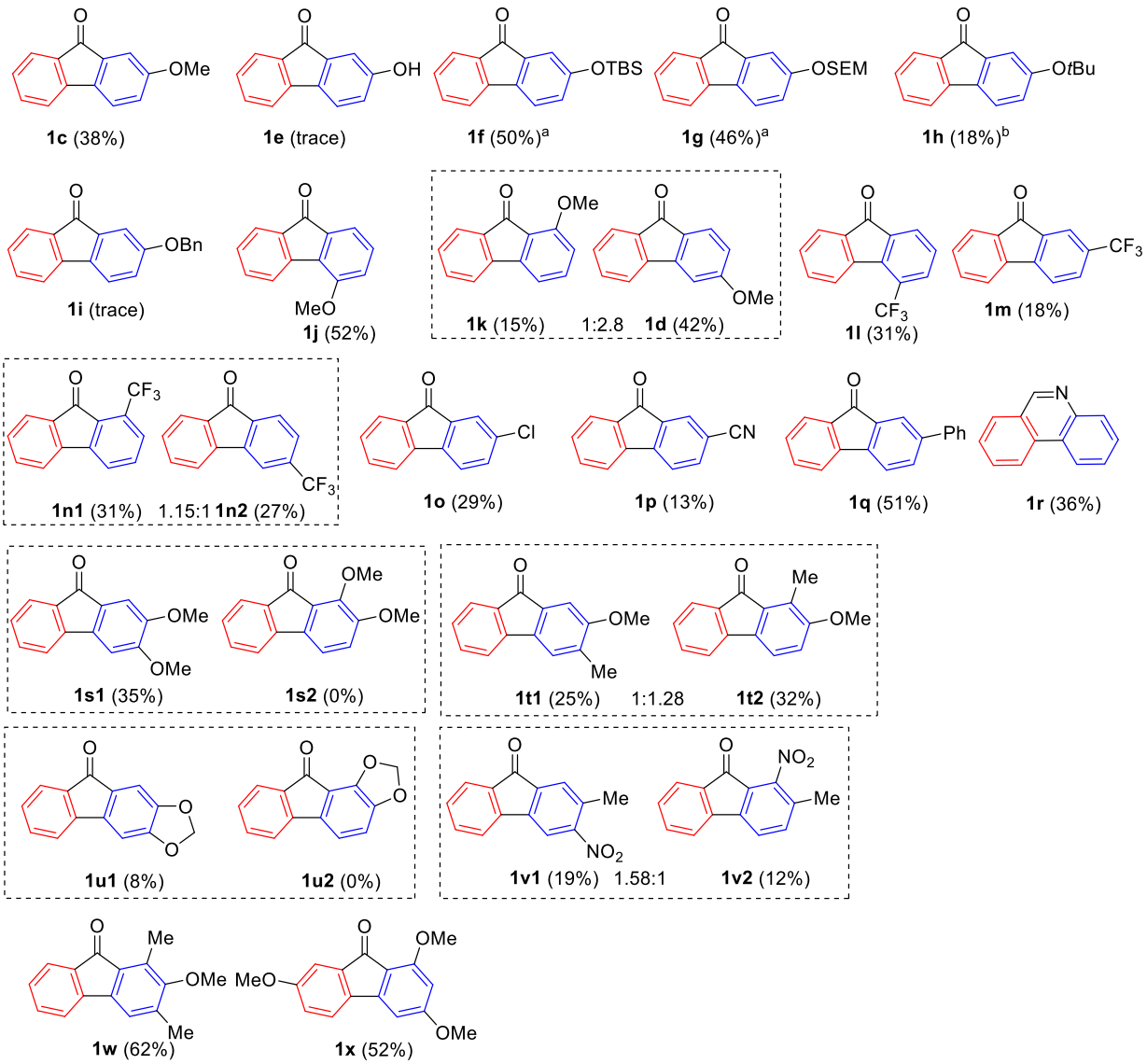
Lastly, synthesis of fluorenone **214** was also attempted following the same general synthesis route (Scheme 92). TBHP-mediated cyclization of benzyl amine **213**, however, went unexpectedly poorly. The steric hindrance between the two methoxy substituents that arises from being forced into spacial vicinity during formation of the planar fluorenone structure might explain the poor yield.



Scheme 92: Total synthesis of compound **214**. Conditions: a) **205**, $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O (1:1), 100 °C, 12 h, 71%; b) TBSCl, imidazole, DMF, 50 °C, 18 h, 88%; c) LAH, $AlCl_3$, THF, 0 °C ⟶ rt, 12 h, 90%; d) $TBHP_{aq}$, 1,2-DCE, 100 °C, 18 h, 4%.

Twenty additional 2-(aminomethyl)biphenyls **184e-x** were cyclized to characterize the scope and limitations of the new fluorenone synthesis protocol (Scheme 93). Substrates bearing substituents susceptible to reduction were hereby prepared by a different route, starting from commercially available 2-bromobenzylamine (**216**), which was Boc-protected to increase its affinity towards subsequent Suzuki cross-coupling. The effect of electron-donating substituents on the radical accepting phenyl ring on the yield of TBHP-mediated cyclization compared to unsubstituted 2-(aminomethyl)biphenyl ranged from slightly adverse to slightly favorable in general with yields of roughly 40-60%. Electron-withdrawing substituents on the radical accepting phenyl ring were generally observed to have an adverse effect on the cyclization yield with yields in the 10-30% range. Substituents at C-4' of the phenyl ring were less favorable than at C-2'. Apart from the amines leading to fluorenones **1s1** and **1u1**, substrates bearing asymmetrically substituted phenyl rings gave a product mixture of compounds with isomeric ratios mostly favoring the sterically less hindered regioisomer. The total cyclization yield of substrates with asymmetrically substituted phenyl rings was usually higher than for symmetrically substituted phenyl rings with substitutents at C-2' and C-4'. Interestingly, anilide **184r** gave phenantridine (**1r**) instead of the expected acetamidofluorenone.

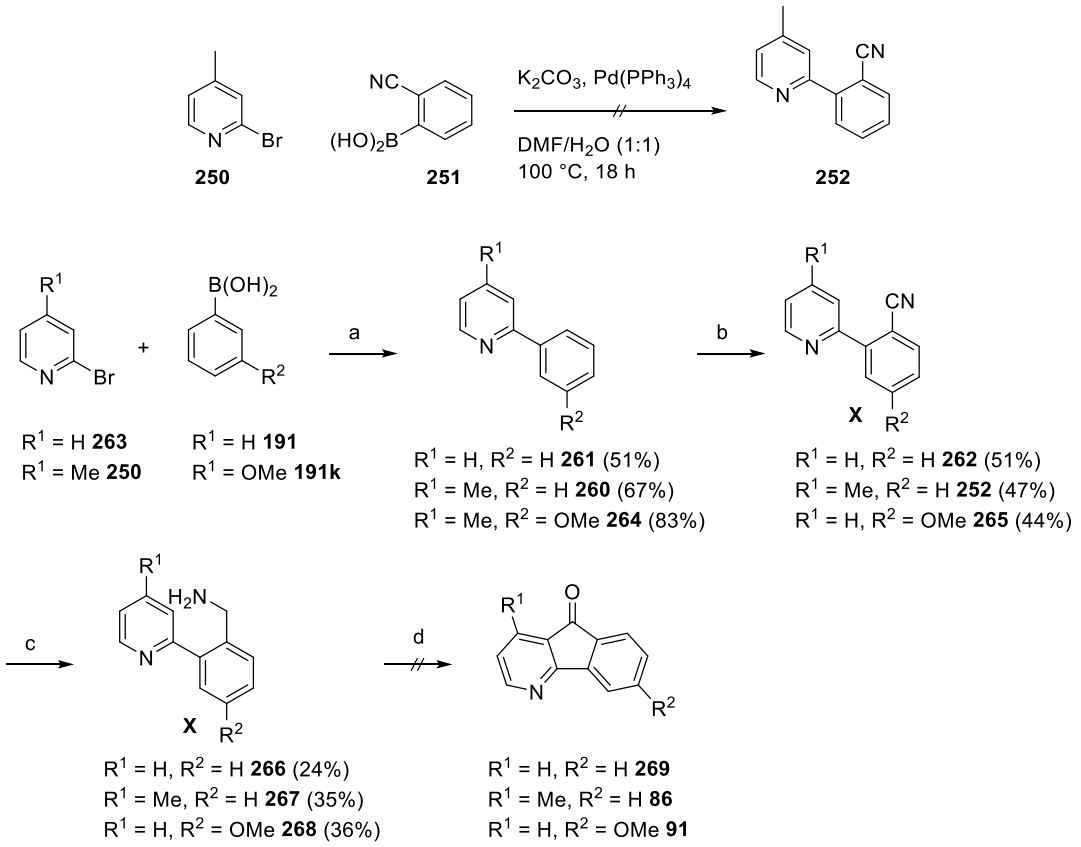




Scheme 93: Substrate scope for the oxidative cyclization of 2-(aminomethyl)biphenyls. Reaction conditions: a) phenylboronic acid **191**, **191e** or **191j-x**, $Pd(PPh_3)_4$, Na_2CO_3 or K_2CO_3, DMF/H_2O, 18 h, 100 °C, 61–99%; b) from **188e** for PG = TBS: TBSCl, imidazole, DMF, 40 °C, 10 h, 88%; c) from **188e** for PG = SEM: SEMCl, DIPEA, THF, rt, 24 h, 57%; d) from **188e** for PG = *t*Bu: $Mg(ClO_4)_2$, Boc_2O, DCM, 40 °C, 24 h, 46%[b]; e) from **188e** for PG = Bn: BnBr, K_2CO_3, THF, rt, 20 h, 96%; f) LAH, $AlCl_3$, THF, 0 °C → rt, 18 h, 39–92%; g) Boc_2O, NEt_3, DCM, rt, 18 h, 89%; h) TFA, DCM, rt, 6 h, 76–98%; i) $TBHP_{aq}$, 1,2-DCE, 100 °C, 18 h (yields in parentheses).[a]approximated yield for product containing compound mixture determined by ^1H NMR; [b]crude yield

5.2 Synthesis of 4-azafluorenones and 4-azafluorenone-type alkaloids

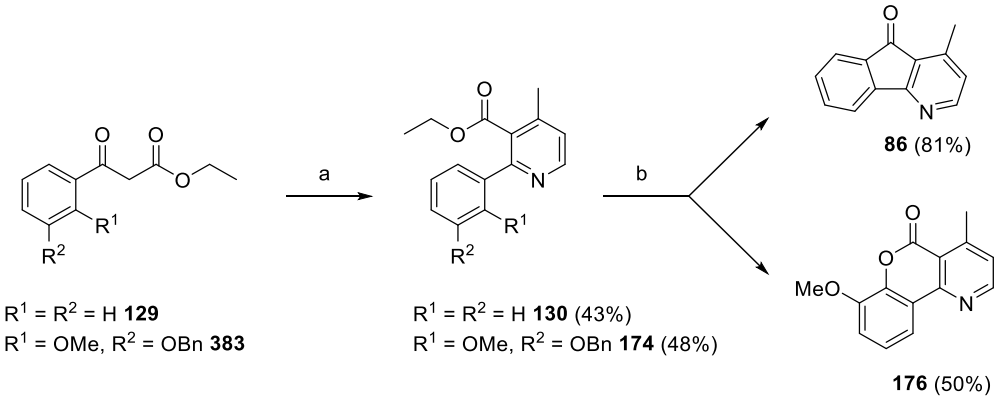
Building on the general synthesis route for the preparation of fluorenones, 4-azafluorenones were to be synthesized by similar means with the final goal of preparing alkaloids of this compound class. Surprisingly, transition metal catalyzed cross-coupling of the appropriate precursors, 2-bromo-4-picoline (**250**) and 2-cyanophenylboronic acid (**251**) failed. However, the same reaction proceeded smoothly in absence of a cyano residue, which was therefore regioselectively introduced after Suzuki coupling by reacting 2-phenylpyridine (**261**) as well as the 2-phenyl-4-picolines **260** and **264** with AIBN and $Cu(OAc)_2$ under an O_2-atmosphere in MeCN at elevated temperatures (Scheme 94). Following nitrile reduction, the respective amines **266**, **267** and **268** were then reacted with TBHP under the established conditions. Unfortunately, none of the experiments yielded the desired 4-azafluorenones.



Scheme 94: Attempted total synthesis of model 4-azafluorenones. Conditions: a) K_2CO_3, $Pd(PPh_3)_4$, DMF/H_2O (1:1), 100 °C, 18 h; b) AIBN, $Cu(OAc)_2$, O_2, MeCN, 135 °C, 24 h; c) LAH, $AlCl_3$, THF, THF, 0 °C → rt, 18 h; d) $TBHP_{aq}$, 1,2-DCE, 100 °C, 18 h (yields in parentheses).

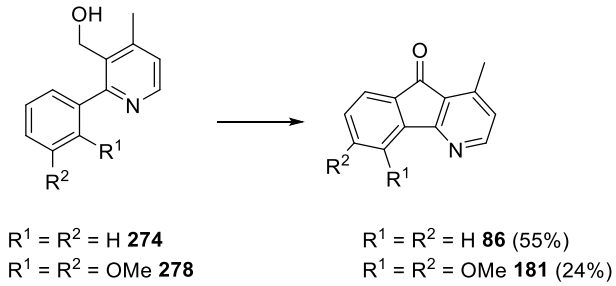
In Scheme **95**, the synthesis for onychine (**86**) and analogues worked out by Franz Bracher as part of his Habilitation thesis is outlined.[151] Hereby, β-ketoester **129** is reacted to the nicotinate ester **130** *via* base-catylzed Michael addition to crotonaldehyde and subsequent intramolecular condensation with hydroxylammonium chloride. Intramolecular Friedel-Crafts-type acylation with PPA furnished onychine (**86**) in the next step. Subjecting 2-(2-

(benzyloxy)phenyl)nicotinate **174** to these conditions, however, gave the lactone **176** as the sole product instead. Later experiments performed by other authors and as part of this thesis would confirm that this behavior also extends to methoxy residues, and therefore most likely alkoxy residues in general.



Scheme 95: Bracher method for the synthesis of 4-azafluorenones.[151] Conditions: a) first NaH, crotonaldehyde, rt, 1,4-dioxane, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min; b) PPA, 130–140 °C (yields given in parentheses).

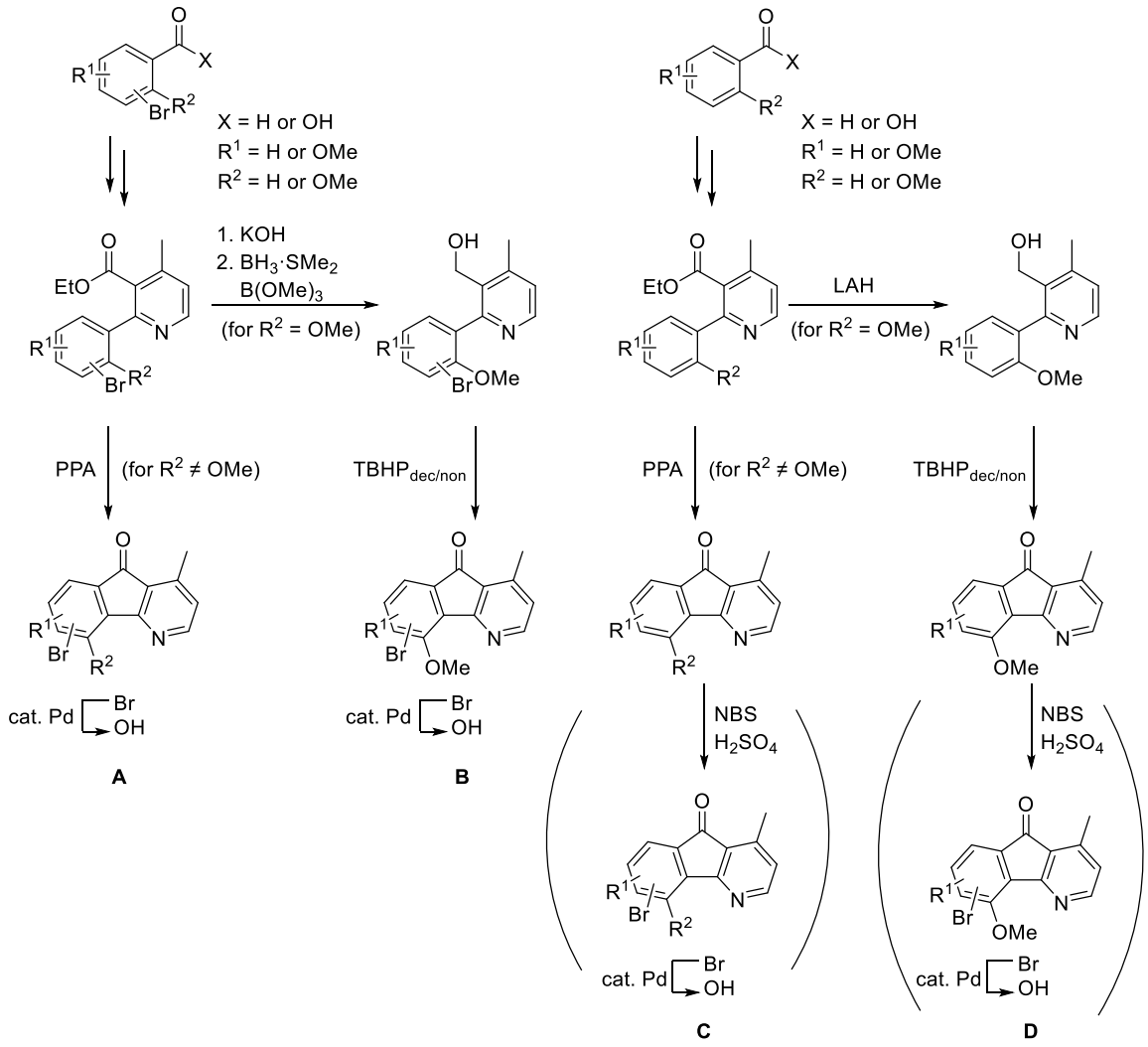
To circumvent undesired lactonization, which prevents the synthesis of 5-oxygenated 4-azafluorenones *via* this convenient pathway, the corresponding pyridinemethanols, accessible *via* reduction of the nicotinate esters with LAH, were to be reacted with TBHP. As a proof of concept, onychine (**86**) was synthesized with this radical method and the alkaloid was furnished with a yield of 55% (Scheme 96). The same reaction performed with the 2',3'-dimethoxy derivative **278** gave 5,6-dimethoxyonychine (**181**), albeit in a low yield of 24%. Nevertheless, formation of the lactone was not observed. A method for the preparation of onychine derivatives bearing 5-alkoxy residues from the corresponding 3-hydroxymethyl-2-phenyl-4-picolines had been established.



Scheme 96: TBHP-mediated cyclization of 2-phenyl-3-pyridinemethanols **274** and **278**.

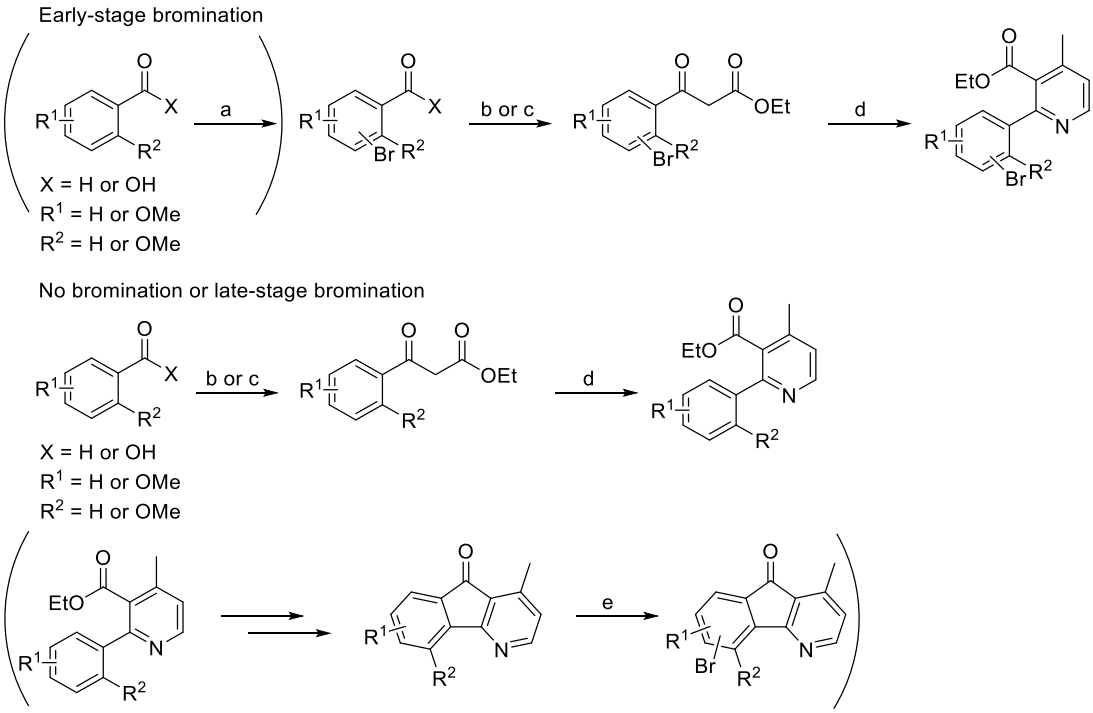
The target 4-azafluorenone alkaloids commonly bear free phenolic hydroxy groups. As to be expected, substrates with unprotected phenolic hydroxy groups were prone to engage in side-reactions in radical-type TBHP-mediated cyclizations. Some of the most commonly employed phenolic protecting groups (Bn, SEM, TBS) proved incompatible with at least one of the diverse reagents and reaction conditions employed throughout the modified Bracher route. Therefore,

a bromide substituent acting as a latent hydroxy group was introduced at appropriate stages and later converted to the respective phenol under Pd-catalysis. In combination with TBHP-mediated cyclization and PPA-mediated cyclization, a general protocol for the synthesis of 4-azafluorenone alkaloids was developed (Scheme 97). Approaches to the total synthesis of 4-azafluorenone alkaloids can be divided into four paths **A**, **B**, **C** or **D** depending on 1) when or if a bromide substituent is introduced and 2) the presence or absence of a 2'-alkoxy residue at the benzenoid ring (exemplarily depicted as OMe in Scheme 97) of the precursor nicotinate.



Scheme 97: General flowchart for the total synthesis of 4-azafluorenone alkaloids.

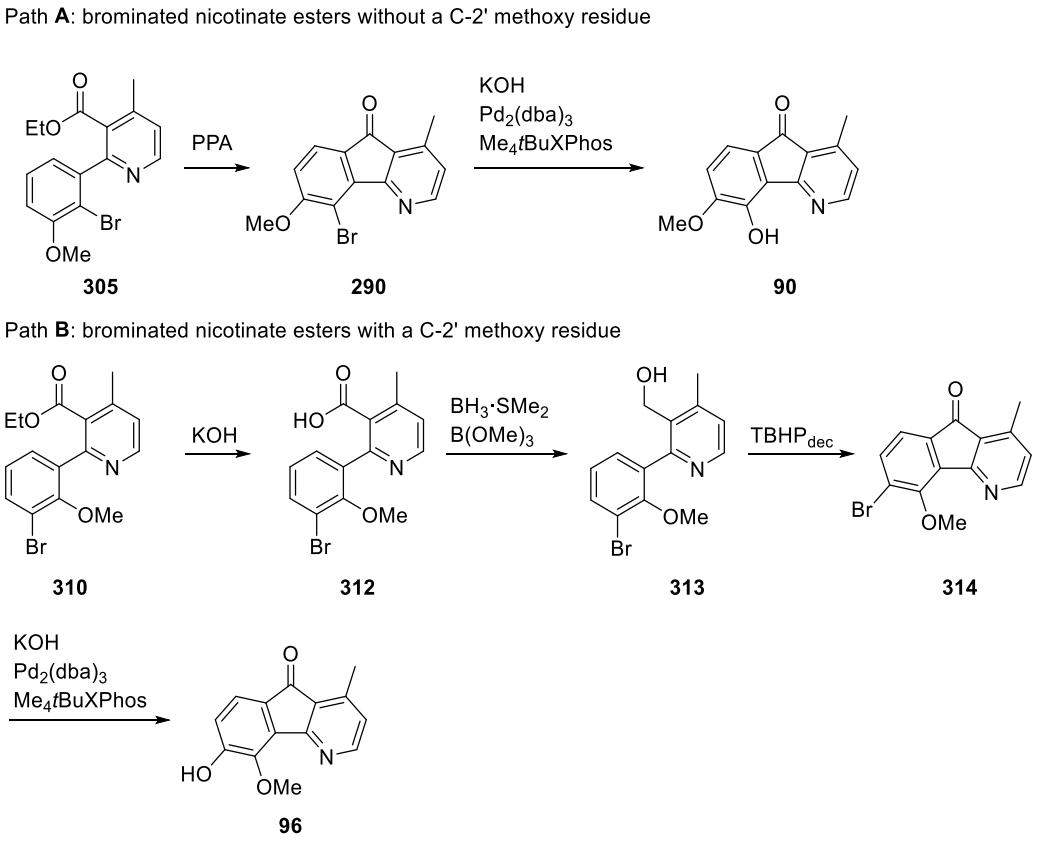
The starting materials were either aldehydes or carboxylic acids that were converted to the respective β-ketoesters (Scheme 98). For conversion of the former, the substrates were reacted with ethyl diazoacetate under $SnCl_2$-catalysis, while in the case of the latter, the substrates were subjected to ethyl potassium malonate and the $MgCl_2$-NEt_3 base system following *in situ* conversion to the acyl chlorides. As previously discussed, the respective β-ketoesters then led to the 2-phenylnicotinate esters in one operation. In this summary, the preparation of precursors will not be further detailed.



Scheme 98: General synthesis route for the preparation of 2-phenylnicotinate intermediates. General conditions: a) NBS, DCM or MeCN, rt, 16-20 h; b) $SnCl_2$, ethyl diazoacetate, DCM, rt, 1 h (for X = H); c) first ethyl potassium malonate, $MgCl_2$, NEt_3, EtOAc, 0 °C → 35 °C, 6 h, then RCOCl derived from carboxylic acid ($SOCl_2$, 2 h, reflux), 0 °C → rt, 18 h (for X = OH); d) first benzyltrimethylammonium hydroxide, crotonaldehyde, 1,4-dioxane, rt, 30 min, then hydroxylammonium chloride, AcOH, 100 °C, 30 min; e) NBS, H_2SO_4, 50 °C, 1.5 h.

From brominated 2-phenylnicotinate intermediates, total synthesis routes branch into two paths. In absence of a methoxy substituent at C-2', the substrate was cyclized to the respective bromofluorenone with PPA and reacted to the alkaloid *via* bromide-to-phenol conversion (Schemes 97 and 99, path **A**). This synthesis route furnished the alkaloid isoursuline (**90**).

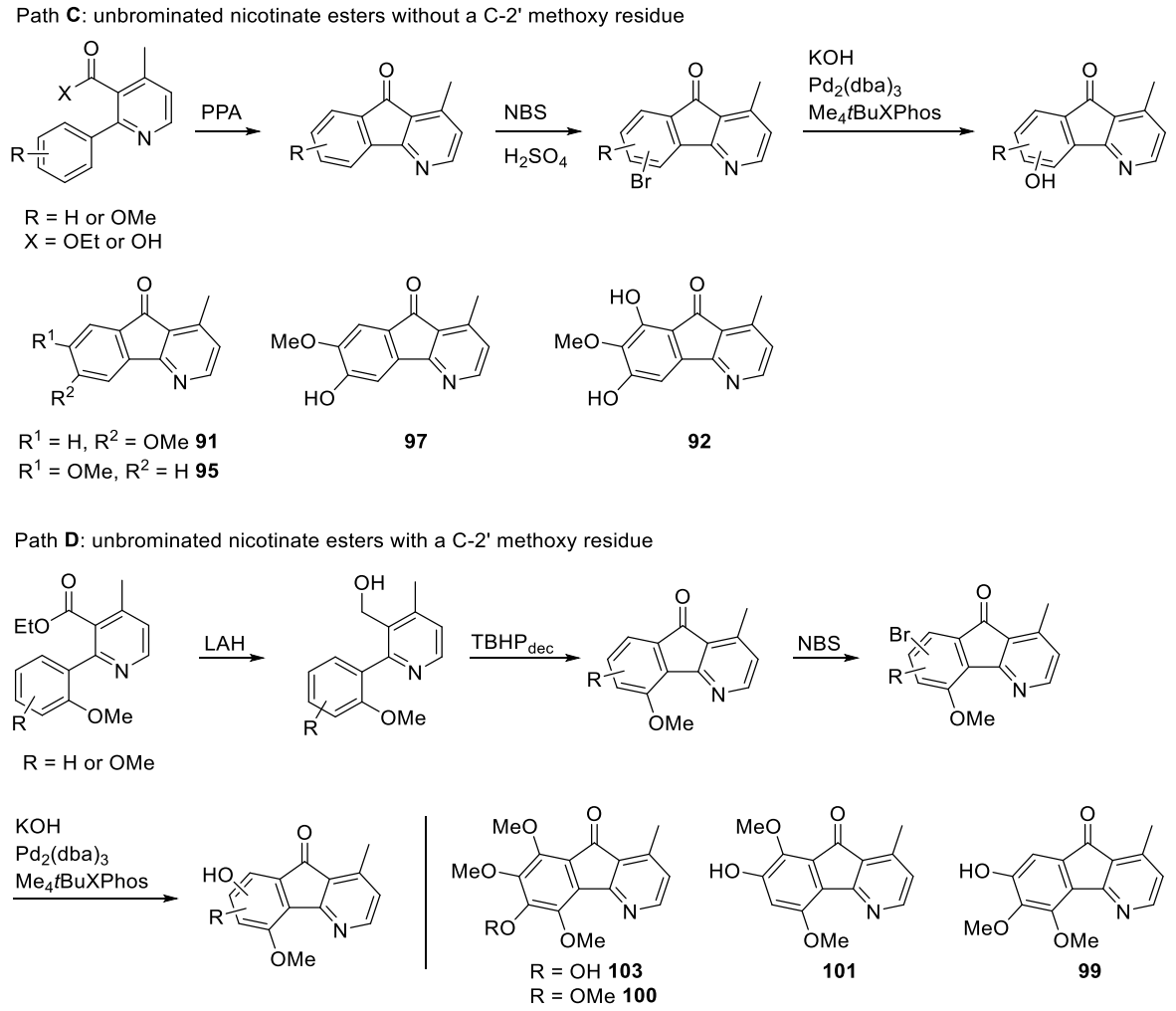
Conversely, in presence of a methoxy substituent at C-2', the nicotinate ester had to be reduced to the pyridinemethanol (Schemes 97 and 99, path **B**). Reductive removal of bromide substituents with complex metal hydride reducing agents such as LAH had to be avoided, so a more suitable two-step reduction was employed. Following alkaline ester hydrolysis, reduction with $BH_3 \cdot SMe_2$ and $B(OMe)_3$ gave the pyridinemethanol without removal of the bromide substituent. Subsequent TBHP-mediated cyclization and bromide-to-phenol conversion furnished the alkaloid ursuline (**96**).



Scheme 99: Synthesis routes for the preparation of 4-azafluorenone alkaloids isoursuline (**90**) and ursuline (**96**) from brominated 2-phenylnicotinate intermediates.

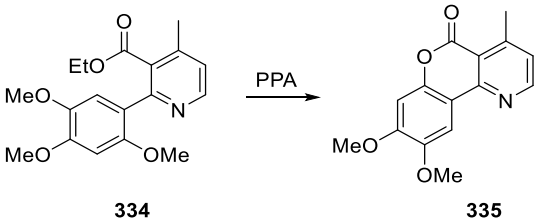
The same logic applies to unbrominated nicotinate esters. Total synthesis routes branch into two paths depending on the presence or absence of a C-2’ methoxy residue and differ in the respective cyclization protocol employed. For unbrominated nicotinate ester precursors without a C-2’ methoxy residue, cyclization was accomplished with PPA (Schemes 97 and 100, path **C**). The corresponding nicotinate ester gave the alkaloid 6-methoxyonychine (**91**). Meanwhile, PPA-mediated cyclization of the carboxylic acid yielded better results than with the nicotinate ester for the preparation of the alkaloid 7-methoxyonychine (**95**). Late-stage bromination of 7-methoxyonychine (**95**) and subsequent bromide-to-phenol conversion furnished the alkaloids oncodine (**97**) and 6,8-dihydroxy-7-methoxyonychine (**92**).

For unbrominated nicotinate ester precursors with a C-2’ methoxy residue, the pyridinemethanols were prepared *via* direct ester reduction with LAH prior to TBHP-mediated cyclization (Schemes 97 and 100, Path **D**). This furnished the alkaloid 5,6,7,8-tetramethoxyonychine (**100**). Bromination of the respective azafluorenone intermediates and bromide-to-phenol conversion gave the alkaloids darienine (**99**), muniranine (**103**) and 7-hydroxy-5,8-dimethoxyonychine (**101**).



Scheme 100: Synthesis routes for the preparation of 4-azafluorenone alkaloids 6-methoxyonychine (**91**), 7-hydroxy-5,6-dimethoxyonychine (**92**), 7-methoxyonychine (**95**), oncodine (**97**), darienine (**99**), 5,6,7,8-tetramethoxyonychine (**100**), 7-hydroxy-5,8-dimethoxyonychine (**101**) and muniranine (**103**) from unbrominated 2-phenylnicotinate intermediates.

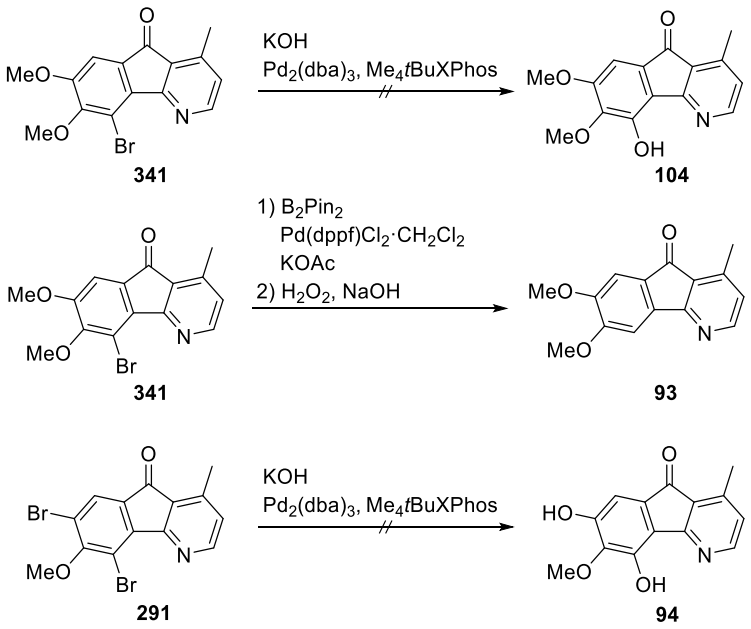
The lactone-type alkaloid polynemoraline C (**335**) was conveniently accessible from the nicotinate ester precursor **334**, which also lead to muniranine (**103**), by exploiting the otherwise undesirable laconization tendency of 2-(2-(alkoxy)phenyl)nicotinates when reacted with PPA (Scheme 101).



Scheme 101: Synthesis of polynemoraline C (**335**).

However, not all total syntheses of alkaloids were successful (Scheme 102). Bromide-to-phenol conversions failed for 5-bromo-6,7-dimethoxyonychine (**341**) and 5,7-dibromo-6-methoxyonychine (**291**) on a preparative scale, although trace amounts of the desired alkaloids cyathocaline (**94**) and 5-hydroxy-6,7-dimethoxyonychine (**104**) were detected *via* ASAP in both

cases. The substrates were either very sluggish to react in the former case or readily consumed in the latter case but did not yield a major product in quantifiable amounts. For 5-bromo-6,7-dimethoxyonychine (**341**), an alternative method was attempted where the bromide was to be first converted into the pinacol boronic ester and subsequently oxidized. However, this method unexpectedly gave the alkaloid polyfothine (**93**) after reductive removal of the bromide substitutent.



Scheme 102: Failed bromide-to-phenol conversions for the attempted synthesis of the alkaloids cyathocaline (**94**) and 5-hydroxy-6,7-dimethoxyonychine (**104**) and unexpected reductive bromide removal during Miyaura borylation of 5-bromoazafluorenone **341** to give polyfothine (**93**).

Conversion of 6,8-dibromo-7-methoxyonychine (**294**) gave the alkaloid oncodine (**97**) as the major product and 6,8-dihydroxy-7-methoxyonychine (**92**) only as the minor product, suggesting that reductive bromide removal at C-8 occurs as a competing reaction. In contrast, conversion of 5-bromo-6-methoxyonychine (**290**) towards isoursuline (**90**) proceeded smoothly. In summary, no clear pattern of reactivity could be established for the bromide-to-phenol conversion of fluorenones with bromide substituents at C-5 and C-8, while conversions at C-6 and C-7 generally worked well.

An overview of all synthesized 4-azafluorenone alkaloids is shown in Scheme 102. Total synthesis of darienine (**99**), 6,8-dihydroxy-7-methoxyonychine (**92**), 5,6,7,8-tetramethoxyonychine (**100**), 7-hydroxy-5,8-dimethoxyonychine (**101**) and muniranine (**103**) has been accomplished for the first time. In addition, 16 unnatural onychine congeners were also prepared.

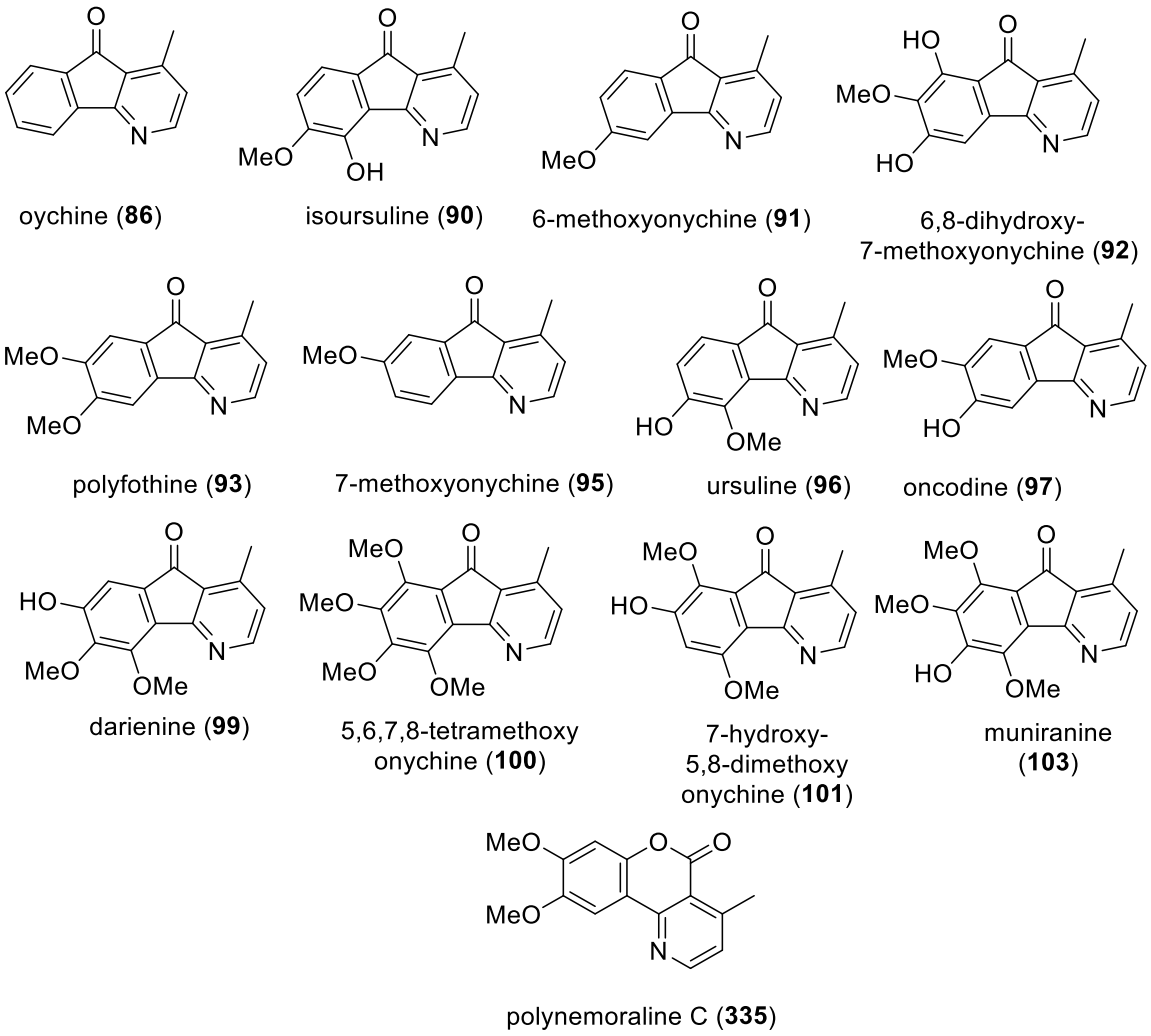


Figure 10: Overview of all synthesized 4-azafluorenone alkaloids and the pyridocoumarin polynemoraline C (**335**).

In summary, a new protocol for the flexible synthesis of fluorenones from substituted *N*-methyl-2-(aminomethyl)biphenyls and 2-(aminomethyl)biphenyls *via* TBHP-mediated cyclization was developed (Figure 11). In total, 25 cyclizations, yielding 25 compounds, were performed with yields in the general range of 30-60%. This reaction tolerates a wide array of functional groups, substitution patterns and some phenol protecting groups such as TBS and SEM. Utilizing this protocol, the first total synthesis of the natural product nobilone (**8**) could be accomplished.

Furthermore, the TBHP-mediated cyclization was also utilized to prepare C-5 oxygenated 4-azafluorenone alkaloids from (2-(2-methoxyphenyl)pyridin-3-yl)methanols. These compounds are inaccessible by more conventionally employed intramolecular Friedel-Crafts-type acylation in highly acidic media of the respective 2-(2-methoxyphenyl)nicotinate precursors, as they show a high tendency towards lactonization. Bromide substituents were hereby introduced at appropriate stages of the synthesis as latent hydroxy groups and later converted under Pd-catalysis, as no conventional phenol protecting groups seemed compatible with the diverse range of reagents and reaction conditions employed in the entire sequence. In combination with PPA-mediated cyclization for substrates insensitive towards lactonization, twelve 4-

azafluorenone natural products were synthesized, including five first total syntheses. The pyridocoumarin-type natural product polynemoraline C (**335**) was also prepared by deliberately exploiting this lactonization.

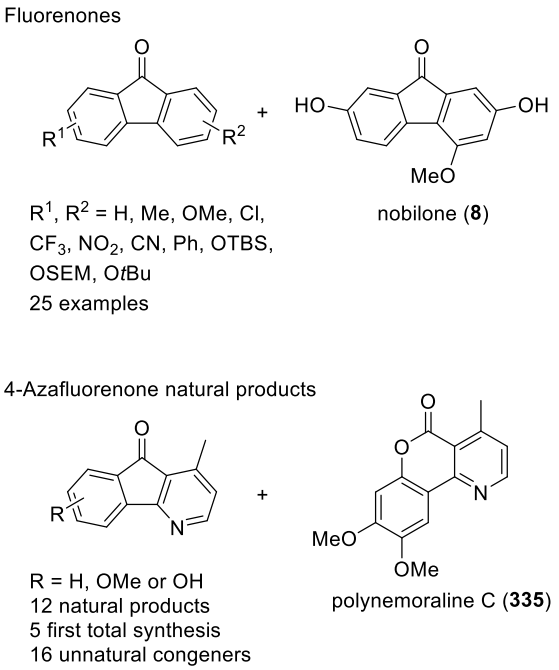


Figure 11: Summary of accomplishments.

Application of this methodology for the total synthesis of azafluoranthenes and bianfugecine (**183**), as a representative of the oxoisoaporphine alkaloid class, was unfortunately unsuccessful.

None of the natural products tested showed noteworthy cytotoxicity in an MTT-assay or biological activity in an agar-diffusion assay

6 Experimental Section

6.1 Materials and methods

Standard laboratory techniques

Reactions sensitive to oxygen and moisture were performed under nitrogen atmosphere with oven- or flame-dried glassware using standard Schlenk line techniques.

Reagents and solvents

Reagents were purchased from chemical vendors including abcr (Karlsruhe, Germany), BLDPharm (Kaiserslautern, Germany.), Merck (Darmstadt, Germany), TCI (Eschborn, Germany) or Th. Geyer (Renningen, Germany). Solvents were either purchased from the aforementioned commercial sources or dried, if necessary, according to standard methods and stored over activated molecular sieves under nitrogen atmosphere.

Protocols for routine biological testing

For the MTT assay, human leukemia HL-60 cells were used. The cell density was determined with a Fuchs-Rosenthal counting chamber and subsequently adjusted to 9 x 10^5 cells *via* dilution. The compounds to be tested were dissolved in DMSO to give 10.0 mM stock solutions, from which (at least) six-fold dilution series with a 1:2 dilution factor were made. Triton X-100 with a final well concentration of 1.00 μg/mL was used as a positive control. For the negative control, 1% DMSO was used. The cell suspensions (99.0 μL) were filled in the wells of a 96-well plate and incubated at 37°C for 24 h with 5% CO_2. Afterwards, the compound solutions (1.00 μL) were added to these wells and the cell suspensions were incubated for an additional 24 h under the same conditions. A MTT solution (10.0 μL of a solution obtained from dissolving 5.00 mg MTT in 1.00 mL PBS) was then added to the cells and they were incubated for an additional 2 h under the usual conditions. Finally, DMSO (190 μL) was added to the wells and they were shaken for 1 h under exclusion of light. The absorption of the wells were then measured photometrically at a wavelength of 570 nm with a MRX Microplate Reader (DYNEX Technologies, Chantilly, USA). Absorbance data analysis and calculations of the IC_{50}-values was performed with the program Prism 4 (GraphPad, La Jolla, USA).

For the agar diffusion assay, fungi and bacteria obtained from Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ, Braunschweig) were used and cultivated in liquid culture according to the instructions provided by DSMZ. For the preparation of the agar plates for *Escherichia coli*, *Pseudomonas marginalis* and *Yarrowia lipolytica*, 35.2 g of all-culture (AC) agar (Merck, Darmstadt, Germany) and 20.0 g agar were suspended in 1.00 L water. For *Staphylococcus equorum* and *Streptococcus entericus*, 10.0 g casein peptone,

5.00 g yeast extract, 5.00 g glucose and 5.00 g sodium chloride were suspended in 1.00 L water. For *Saccharomyces cerevisiae*, 35.2 g AC agar was suspended in water (1.00 L). After the suspensions were autoclaved, 15.0 mL of each were poured into petri dishes under aseptic conditions and they were cooled to 8 °C for 1 h. The compounds to be tested were dissolved in DMSO to give 1% (m/V) solutions. Each solution (3.00 μL) was applied to filter plates (d = 6.00 mm, Macherey-Nagel) in volumes containing 30.0 μg of substance. Tetracycline (antibacterial) and clotrimazole (antifungal) were used as positive controls. A filter plate with DMSO was used as a negative control. The filter plates were dried for 24 h at room temperature before applying them to the agar plates. After initial preparations, the germs were then applied to the agar plates using cotton swabs. The platelets containing compound to be tested, reference substances and the blind control were put on to the agar. The agar plates were then incubated at 32 °C (bacteria) or 28 °C (yeast) for 36 h. Finally, the diameters of the resulting inhibition zones were measured manually in case they had formed.

Both assays were performed by Matina Stadler (AK Bracher).

Characterization and analytical techniques

Melting points were measured with open capillary tubes and a Büchi Schmelzpunktapparatur B-540 and are reported in °C. NMR spectra (^{1}H 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 (^{1}H NMR:400 MHz and 500 MHz, ^{13}C NMR: 101 MHz and 126 MHz) and using 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. Infrared spectra were recorded from 4000 to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 FTR-IR instrument. For detection, a Smiths Detection DuraSamp IR II Diamond ATR sensor was used. The absorption bands are reported in wave number (cm^{-1}). High-resolution mass spectrometry (HRMS) was performed by the LMU Mass Spectrometry Service using a Thermo Finnigan MAT 95 or a Jeol MStation 700 or JMS GCmate II Jeol instrument at 250 °C and 70 eV for electron impact ionization (EI). A Thermo Finnigan LTQ Ultra Fourier Transform Ion Cyclotron Resonance device at 250 °C was used for electrospray ionization (ESI).

Qualitative reaction control

All reactions were monitored *via* thin-layer chromatography using POLYGRAM SIL G/UV254 polyester sheets coated with SiO_2 (0.2 mm, 40 x 80 mm, Macherey-Nagel) and visualized by UV light irradiation at 254 nm and 366 nm. For the visualization of primary and secondary amines, the respective on TLC-plates were dipped into a ninhydrin stain (0.100 g ninhydrin,

0.500 mL AcOH, 100 mL acetone) and subsequently heated with a heat gun. Following standard work-up, crude reaction mixtures were analyzed *via* atmospheric solids analysis probe (ASAP) coupled with an expression Compact Mass Spectrometer (CMS, Advion, Ithaca, USA). Unstained TLC plates were also analyzed *via* direct mass analysis with a Plate Express™ automated TLC plate reader combined with a CMS (Advion, Ithaca, USA). Atmospheric pressure chemical ionization (APCI) was used as the ionization method.

Purification

Crude products were purified *via* flash column chromatography (FCC) and preparative TLC. FCC was performed using silica gel Si 60 (0.040 – 0.063 mm, 230 – 400 mesh ASTM, Merck, Darmstadt, Germany). For preparative TLC, PLC Silica gel 60 F_{254}, 2 mm glass plates 20 x 20 cm (Merck, Darmstadt, Germany) were used.

Gas chromatography

For the determination of the temperature-programmed Kováts retention indices, alkane standards C7–C30 saturated (1000 mg/mL in *n*-hexane), alkane standard C10–C40 (all even, 50 mg/mL in *n*-heptane), as well as HPLC grade acetonitrile purchased from Merck (Schnelldorf, Germany) were used. The internal standard **IS** fluorene was purchased from HPC Standards GmbH (Cunnersdorf, Germany). Stock solutions of each compound (1 mg/mL) were prepared in acetonitrile and stored at 4 °C. Working solutions (in acetonitrile) for each experiment were prepared in following concentrations: compounds **82**, **84**, **86**, **90**, **91**, **93**, **95**, **96**, **99**–**101**, **103**, **182**, **183**, **335**, **337**, **359**, **360**, **363**, **364** and **IS** at 20 μg/mL; compounds **361** and **362** at 50 μg/mL; compounds **356**–**358** 100 μg/mL.

Gas chromatography (GC) was performed with a 7820A gas chromatograph from Agilent Technologies (Santa Clara, CA, USA). The G4514A autosampler and the G4513A injector were from Agilent Technologies (Santa Clara, CA, USA). Instrument control and data analysis were carried out with a Masshunter 8.0 from Agilent. An HP-5-ms capillary column of 30 m length, 0.25 mm i.d., and 0.25 μm film thickness was used at a constant flow rate of 1.2 mL/min. Helium 99.999% from Air Liquide (Düsseldorf, Germany) was used as carrier gas. The inlet temperature was kept at 300 °C and the injection volume was 2 μL with splitless time 0.5 min. The initial column temperature was 50 °C and was held for 1 min. Then, temperature was ramped up to 320 °C (10 °C/min) and held for 2 min. The total run time was 30 min. MS source temperature was 230 °C and quadrupole temperature was 150 °C. The MS was operated with electron ionization (EI) at 70 eV in scan mode (m/z 40–600) with a solvent delay of 7.0 min. Gas chromatography was performed by Christoph Müller and Carolin Bauernschmidt.

HPLC Purity Methods

HPLC analytical measurements for the determination of the purities of the compounds were carried out detecting at 210 nm and 254 nm using the following methods:

Method 1:

Zorbax Eclipse Plus, C18 5.0 µm (4.6 x 150 mm), injection vol. 5-10 µL, temp. 35-50 °C

Eluents: a) (MeCN+0.1% formic acid)/water 50:50; flow 1.2 mL/min

b) MeCN/water 50:50; flow 1.5 mL/min

c) (MeCN+0.1% formic acid)/water 30:70; flow 1.2 mL/min

d) MeOH/water 65:35; flow: 1.2 mL/min

Method 2:

Trudel Eclipse Plus, C18 5.0 µm (4.6 x 150 mm) USUXB17231

Eluents: a) MeCN/water 40:60; injection vol. 5 µL, flow rate 1.5 mL/min, temp. 30 °C

b) MeOH/water 65:35; injection vol. 10 µL, flow rate 1.2 mL/min, temp. 35 °C

Method 3:

Poroshell 120, EC-C18 2,7µm 4,6 x 50 mm

Eluents: a) MeOH/water 50:50; injection vol. 5 µL, flow rate 1.0 mL/min, temp. 35 °C

b) MeOH/water 60:40; injection vol. 2 µL, flow rate 0.8 mL/min, temp. 35 °C

6.2 General synthetic procedures

6.2.1 General procedure A1: TBHP-mediated cyclization of *N*-methyl-2-(aminomethyl)biphenyls and 2-(aminomethyl)biphenyls

Aqueous TBHP (70%, 4.0 equiv.) was added to a solution of primary amine or secondary amine (1.0 equiv.) in 1,2-DCE (4.0 mL per mmol amine) in a vial lined with a teflon cap and the resulting mixture was heated to 100 °C for 18 h. The solvent was evaporated *in vacuo* and the crude product purified by FCC without further workup.

6.2.2 General procedure A2: TBHP-mediated cyclization of (4-methyl-2-phenylpyridin-3-yl)methanols

TBHP in nonane or decane (5.5 M, 4.0 equiv.) was added to a solution of pyridinemethanol (1.0 equiv.) in 1,2-DCE (4.0 mL per mmol alcohol) in a vial lined with a teflon cap and the resulting mixture was heated to 100 °C for 18-30 h. The solvent was evaporated *in vacuo* and the crude product purified by FCC on silica gel without further workup.

6.2.3 General procedure B: Bromide-to-phenol conversion

In accordance with the method developed by the Buchwald group[206], a glass tube with an aluminium cap and septum containing a stir bar was charged with alcohol (1.0 equiv.) Pd_2dba_3

(4.0 mol% Pd), 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 organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by FCC on silica gel.

6.2.4 General procedure C: PPA-mediated cyclization

A flame-dried flask was charged with ester and PPA (10 mg per mg ester) under nitrogen atmosphere and the mixture was heated to 150 °C for 1.5 h under vigorous stirring. The reaction was then hydrolyzed with water under ice-cooling, and the resulting suspension extracted with EtOAc. The organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by FCC on silica gel.

6.2.5 General procedure D: Hydrolysis of esters to give carboxylic acids

KOH (4.0 equiv.) was added to a solution of ester (1.0 equiv.) dissolved in a mixture of ethanol and water (2:1, 10 mL per mmol ester) and the resulting solution was heated to reflux overnight. After cooling to room temperature, the ethanol was removed *in vacuo*. Additional water was added to the concentrate and the solution was acidified to pH 5-6, and the resulting precipitate was filtered and washed with water. The crude product was further purified *via* FCC.

6.2.6 General procedure E: Synthesis of 2-phenylnicotinic acid esters

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 nitrogen atmosphere and the resulting solution was stirred for 30 minutes. Hydroxylammonium chloride and AcOH (1.0 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 was observed. The mixture was extracted with EtOAc and the combined organic phases were washed with water and brine. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified *via* FCC.

6.2.7 General procedure F: Ring bromination of azafluorenones

In accordance with the method developed by Młochowski and Szulc[204], NBS (1.1 equiv.) was added to a solution of azafluorenone (1.0 equiv.) in concentrated sulfuric acid (10 mL per mmol azafluorenone) in a preheated oil-bath at 50 °C under vigorous stirring. After 1 h, the reaction mixture was poured into water and alkalized with concentrated aqueous ammonia solution until

a precipitate formed. The suspension was extracted with EtOAc, the organics washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by FCC on silica gel.

6.2.8 General procedure G: Suzuki coupling

Boronic acid (1.5 equiv.), (hetero)aryl halide (1.0 equiv.), palladium catalyst (5.0 mol% of $Pd(PPh_3)_4$, or $Pd(OAc)_2$ in combination with 0.20 equiv. of a phosphine ligand), and Na_2CO_3 (3.0 equiv.) were dissolved in a mixture of H_2O/DMF (1:1, 10 mL per mmol 2-bromobenzonitrile or 2-bromo-*N*-Boc-benzylamine) under nitrogen atmosphere. The resulting heterogeneous mixture was refluxed for 18 h, before it was diluted with H_2O. The mixture was extracted with EtOAc, the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by FCC.

6.2.9 General procedure H: Reduction of nitriles to give primary amines

$AlCl_3$ (1.5 - 4.0 equiv.) was carefully added to a stirred suspension of LAH (1.5 - 4.0 equiv.) in anhydrous THF (10 mL per mmol nitrile) at 0 °C. The reaction mixture was then stirred vigorously for 20 min before a solution of biphenyl-2-carbonitrile (1.0 equiv.) in THF was added dropwise, after which stirring was continued for 16 h. In case the reaction was not complete (TLC control), additional LAH and $AlCl_3$ were added. After completion of the reaction, it was quenched by slowly adding H_2O. The mixture was concentrated *in vacuo*. 1 M NaOH was added to the residue and stirred until a white solid formed. Then the mixture was filtered through a pad of silica gel, and the filtrate was extracted with EtOAc and washed with H_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by FCC.

6.2.10 General procedure I: Boc deprotection of amines

Trifluoroacetic acid (TFA) (26-32 equiv.) was added to a solution of *N*-Boc-protected amine (1.0 equiv.) dissolved in DCM (10 mL per mmol amide) and the mixture was stirred for 6 h at room temperature. After completion of the reaction the solvent was evaporated *in vacuo*. Aqueous NaOH (1 M) was added to the residue, followed by extraction with EtOAc. The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by FCC.

6.2.11 General procedure J: TBS protection of phenols

Imidazole (2.5 equiv.) and TBSCl (1.2 equiv.) were added to a solution of phenol (1.0 equiv.) in DMF (10 mL per mmol phenol) at 50 °C and stirred for 16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with Et_2O, and the organic layer was separated from the aqueous layer. The aqueous layer was extracted

with Et_2O, and the combined organic layers were washed with H_2O, LiCl solution (5 %) and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by FCC.

6.2.12 General procedure K: SEM protection of phenols

The phenol (1.0 equiv.) was dissolved in dry THF (10 mL per mmol phenol) and DIPEA (5.0 equiv.) or NaH (1.5 equiv.) was added, followed by slow addition of the SEMCl (1.4 - 3.0 equiv.). The mixture was stirred at room temperature overnight, then poured into a H_2O-ice mixture (20 mL). The mixture was extracted with Et_2O, and the combined organic layers were washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by FCC.

6.2.13 General procedure L: Benzyl protection of phenols

Benzyl bromide (1.2 equiv.) and K_2CO_3 (2.0 equiv.) was added to a solution of phenol (1-0 equiv.) in THF (10 mL per mmol phenol) and stirred for 16-20 h at rt. After completion of the reaction, the solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with water and brine. The organic phase was dried with $MgSO_4$ and the solvent was reduced *in vacuo*. The crude product was purified by FCC.

6.2.14 General procedure M: Synthesis of boronic acids

A solution of *n*-butyllithium (2.5 M, 1.1 equiv.) in hexane was added dropwise to a solution of phenylbromide (1.0 equiv.) in THF (10 mL per mmol bromide) under nitrogen atmosphere at -78 °C. The mixture was stirred for 1.5 h after which $B(O\textit{i}Pr)_3$ (1.2 equiv.) was added. The mixture was stirred for an additional 2.5 h and then quenched with a solution of saturated NH_4Cl. After allowing the mixture to warm to room temperature water was added. The pH was adjusted to ~5.0 with 1 M HCl and the resulting solution extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by FCC.

6.2.15 General procedure N: Ring bromination of benzenoid precursors

NBS (1.1 equiv.) was added portionwise to a solution of starting material in various solvents including DCM and MeCN (10 mL per mmol substrate). The reaction mixture was stirred for 16-20 h. In case the starting material was not completely consumed at this point, the reaction mixture was warmed to 60 °C and stirred for an additional 16-20 h and additional NBS was added portionwise. After completion of the reaction, the solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with water and brine. The organic phase was dried with $MgSO_4$ and the solvent was reduced *in vacuo*. The crude product was purified by FCC on silica gel.

6.2.16 General procedure O: *O*-Methylation of phenols

K_2CO_3 (2.0 equiv.) and MeI (1.1 equiv.) were added subsequently to a solution of phenol in DMF (10 mL per mmol phenol). The mixture was stirred at rt overnight. After the reaction had completed, the mixture was poured into diluted HCl and extracted with EtOAc. The organic phases were washed with water and brine, dried with $MgSO_4$, and then filtered and concentrated *in vacuo*. The crude product was purified by FCC on silica gel.

6.2.17 General procedure P: Directed C-H cyanation of 2-phenylpyridines

In accordance with the method developed by Xu and coworkers[188], a pressure tube was charged with 2-phenylpyridine (1.0 equiv.), AIBN (5.0 equiv.) and $Cu(OAc)_2$ (1.1 equiv.) was evacuated under high vacuum and backfilled with O_2 three times. MeCN (10 mL per mmol 2-phenylpyridine) was injected *via* syringe. The tube was sealed with a Teflon lined screwcap. The reaction was stirred at 135 °C for 24 h before the solvent was concentrated *in vacuo*. The crude product was purified by FCC on silica gel.

6.2.18 General procedure Q: Reduction of esters to give primary alcohols

LAH (2.0 equiv.) was added to a solution of ester (1.0 equiv.) in dry THF (10 mL per mmol ester), and the mixture was stirred overnight. In case the reaction hadn't completed, additional LAH (2.0 equiv.) was added. Once the reaction had completed, the reaction was quenched by adding MeOH dropwise, followed by water until no further gas evolution was observed. The suspension was stirred an additional 30 minutes, filtered, and concentrated *in vacuo*. The resulting mixture was extracted with EtOAc, and the combined organic phases were washed with water and brine. The combined organics were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified *via* FCC.

6.2.19 General procedure R1: Synthesis of β-ketoesters (1)

In accordance with the methods developed by Holmquist and Roskamp[198] and Yadav et al.[201], a Schlenk flask was charged with either $SnCl_2$ or $NbCl_5$ (0.25 equiv.) under nitrogen atmosphere after which dry DCM (10 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 stirred at rt until gas evolution stopped. The suspension was filtered, the filter cake washed with DCM and the filtrate evaporated *in vacuo* to give the crude product. The crude product was purified *via* FCC.

6.2.20 General procedure R2: Synthesis of β-ketoesters (2)

Carboxylic acid (1.0 equiv.) was dissolved in DCM or toluene (10 mL per mmol carboxylic acid). After adding $SOCl_2$ (1.5–10 equiv.), the mixture was heated to reflux. After 2 h, the volatiles were removed *in vacuo*.

In accordance with the method developed by Clay and coworkers[202], NEt_3 (2.2-3.5 equiv.) and $MgCl_2$ (1.7-2.5 equiv.) were added to a mixture of ethyl potassium malonate (1.3-1.5 equiv.) in EtOAc (10 mL per mmol acid chloride) at 0 °C under nitrogen atmosphere. The mixture was then stirred at 35 °C for 6 h. After cooling the reaction 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 dropwise to ~pH = 4. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were washed with HCl followed by H_2O and then concentrated *in vacuo*. The crude product was purified *via* FCC.

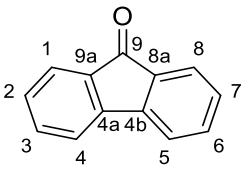
Most β-ketoesters prepared with **General procedure R1** and **R2** afforded mixtures of keto-enol tautomers.

6.2.21 General procedure S: Reduction of carboxylic acids to give primary alcohols

Borane-dimethylsulfide (3.0 equiv.) and trimethyl borate (3.0 equiv.) were added to carboxylic acid (1.0 equiv.) in dry THF (10 mL per mmol carboxylic acid) at 0 °C under nitrogen atmosphere. The resulting solution was stirred at rt for 18 h, cooled to 0 °C, quenched with MeOH and concentrated *in vacuo*. 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 combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by FCC on silica gel.

6.3 Compound preparation and analytical data

9*H*-Fluoren-9-one (1)



$C_{13}H_8O$

M = 180.2060 g/mol

This compound was prepared in accordance with **General procedure A1** and **A2** from different starting materials:

a) from secondary amine **173** (90.7 mg, 0.460 mmol) and aqueous TBHP (70%, 0.255 mL, 1.84 mmol). Purification by FCC afforded the product **1** as a yellow solid (50.0 mg, 0.277 mmol, 60%).
b) from primary amine **184** (134 mg, 0.730 mmol) and aqueous TBHP (70%, 0.404 mL, 2.92 mmol). Purification by FCC afforded the product **1** as a yellow solid (83.0 mg, 0.461 mmol, 62%).
c) from primary amine **184** (119 mg, 0.650 mmol) and TBHP in decane (80%, 0.315 mL, 2.60 mmol). Purification by FCC afforded the product **1** as a yellow solid (26.3 mg, 0.146 mmol, 22%).
d) from alcohol **186** (92.1 mg, 0.500 mmol) and aqueous TBHP (70%, 0.277 mL, 2.00 mmol). Purification by FCC afforded the product **1** as a yellow solid (23.2 mg, 0.128 mmol, 26%).
e) from alcohol **186** (97.6 mg, 0.530 mmol) and TBHP in decane (80%, 0.257 mL, 2.12 mmol). Purification by FCC afforded the product **1** as a yellow solid (57.0 mg, 0.316 mmol, 60%).
f) from aldehyde **187** (87.5 mg, 0.480 mmol) and aqueous TBHP (70%, 0.266 mL, 1.92 mmol). Purification by FCC afforded the product **1** as a yellow solid (21.9 mg, 0.122 mmol, 25%).
g) from aldehyde **187** (95.0 mg, 0.520 mmol) and TBHP in nonane (5.5 M, 0.378 mL, 2.08 mmol). Purification by FCC afforded the product **1** as a yellow solid (24.4 mg, 0.133 mmol, 26%).
h) from tertiary amine **189** (133 mg, 0.560 mmol) and aqueous TBHP (70%, 0.310 mL, 2.24 mmol). Purification by FCC afforded the product **1** as a yellow solid (13.5 mg, 0.0750 mmol, 13%).

R_f: 0.46 (hexanes/EtOAc 12:1).

M.p.: 81 – 82 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.63 (ddd, J = 7.3, 1.2, 0.8 Hz, 2H, 1-H and 8-H), 7.57 (ddd, J = 7.5, 1.2, 0.8 Hz, 2H, 4-H and 5-H), 7.51 (td, J = 7.4, 1.2 Hz, 2H, 3-H and 6-H), 7.31 (dd, J = 7.4, 1.2 Hz, 2H, 2-H and 7-H).

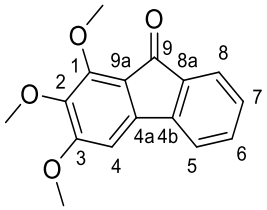
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 194.0 (C-9), 144.8 (C-4a and C-4b), 135.1 (C-3 and C-6), 134.5 (C-8a and C-9a), 129.5 (C-2 and C-7), 124.4 (C-1 and C-8), 120.8 (C-4 and C-5).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2365, 2343, 1715, 1611, 1599, 1450, 1299, 1193, 1151, 1098, 919, 736, 671.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{13}H_8O^{\bullet+}$: 180.0575; found 180.0569.

Literature known compound.[241]

1,2,3-Trimethoxy-9*H*-fluoren-9-one (1a)



$C_{16}H_{14}O_4$

M = 270.2840 g/mol

This compound was prepared from in accordance with **General procedure A1** from

a) secondary amine **173a** (90.2 mg, 0.314 mmol) and aqueous TBHP (70%, 0.174 mL, 1.26 mmol). Purification by FCC afforded the product **1a** as a yellow solid (58.0 mg, 0.215 mmol, 67%).
b) primary amine **184a** (120 mg, 0.440 mmol) and aqueous TBHP (70%, 0.244 mL, 1.76 mmol). Purification by FCC afforded the product **1a** as a yellow solid (61.0 mg, 0.226 mmol, 50%).

R_f: 0.27 (hexanes/EtOAc 4:1).

M.p.: 100 – 101 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.54 (dt, J = 7.3, 0.9 Hz, 1H, 8-H), 7.48 – 7.45 (m, 2H, 5-H and 6-H), 7.27 (ddd, J = 7.3, 5.6, 2.7 Hz, 1H, 7-H), 6.89 (s, 1H, 4-H), 4.07 (s, 3H, 1-OCH_3), 3.98 (s, 3H, 3-OCH_3), 3.81 (s, 3H, 2-OCH_3).

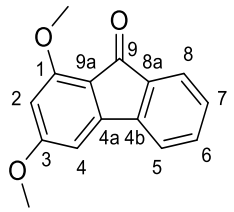
^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 190.8 (C-9), 160.0 (C-3), 154.0 (C-1), 143.5 (C-4b), 142.7 (C-4a), 142.5 (C-2), 135.8 (C-13), 134.4 (C-6), 129.3 (C-7), 123.9 (C-8), 120.0 (C-5), 118.5 (C-9a), 100.7 (C-4), 62.5 (1-OCH_3), 61.7 (2-OCH_3), 57.0 (3-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3006, 2980, 2944, 2838, 1705, 1607, 1590, 1485, 1465, 1412, 1377, 1254, 1208, 1136, 975, 760.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{16}H_{14}O_4^{\bullet+}$: 270.0892; found 270.0885.

Literature known compound.[242]

1,3-Dimethoxy-9*H*-fluoren-9-one (1b)



$C_{15}H_{12}O_3$

M = 240.2580 g/mol

This compound was prepared in accordance with **General procedure A1** from

a) secondary amine **173b** (43.0 mg, 0.167 mmol) and aqueous TBHP (70%, 0.0925 mL, 0.668 mmol). Purification by FCC afforded the product **1b** as a yellow solid (24.0 mg, 0.100 mmol, 59%).
b) primary amine **184b** (77.9 mg, 0.320 mmol) and aqueous TBHP (70 %, 0.177 mL, 1.28 mmol). Purification by FCC afforded the product **1b** as a yellow solid (70.4 mg, 0.290 mmol, 92%).

R_f: 0.29 (hexanes/EtOAc 2:1).

M.p.: 141 – 142 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.55 (dt, *J* = 7.3, 1.1 Hz, 1H, 8-H), 7.52 – 7.49 (m, 1H, 5-H), 7.46 (td, *J* = 7.4, 1.1 Hz, 1H, 6-H), 7.31 (td, *J* = 7.3, 1.1 Hz, 1H, 7-H), 6.74 (d, *J* = 1.9 Hz, 1H, 4-H), 6.31 (d, *J* = 1.9 Hz, 1H, 2-H), 3.94 (s, 3H, 3-OCH_3), 3.92 (s, 3H, 1-OCH_3).

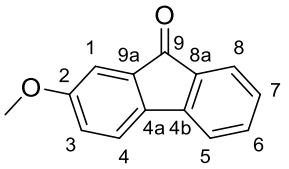
^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 190.5 (C-9), 168.0 (C-3), 160.6 (C-1), 149.0 (C-4a), 142.9 (C-4b), 136.2 (C-8a), 133.9 (C-6), 129.9 (C-7), 123.6 (C-8), 120.6 (C-5), 114.4 (C-9a), 100.2 (C-4), 98.5 (C-2), 56.5 (1-OCH_3), 56.4 (3-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2972, 2874, 1697, 1615, 1602, 1466, 1380, 1308, 1211, 1147, 1029, 768.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{12}O_3^{\bullet+}$: 240.0786; found 240.0782.

Literature known compound.[243]

2-Methoxy-9*H*-fluoren-9-one (1c)



$C_{14}H_{10}O_2$

M = 210.2320 g/mol

This compound was prepared in accordance with **General procedure A1** from

a) secondary amine **173c** (132 mg, 0.581 mmol) and aqueous TBHP (0.322 mL, 2.33 mmol). Purification by FCC afforded the product **1c** as a yellow solid (41.0 mg, 0.195 mmol, 34%).
b) primary amine **184c1** (113 mg, 0.530 mmol) and aqueous TBHP (70%, 0.293 mL, 2.12 mmol). Purification by FCC afforded the product **1c** as a yellow solid (45.0 mg, 0.214 mmol, 40%).
c) primary amine **184c2** (102 mg, 0.480 mmol) and aqueous TBHP (70%, 0.266 mL, 1.92 mmol). Purification by FCC afforded the product **1c** as a yellow solid (38.0 mg, 0.181 mmol, 38%).

R_f: 0.38 (hexanes/EtOAc 10:1).

M.p.: 72 – 73 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.56 (dt, *J* = 7.4, 1.0 Hz, 1H, 8-H), 7.48 – 7.42 (m, 3H, 4-H and 5-H and 6-H), 7.21 (ddd, *J* = 7.4, 6.0, 2.6 Hz, 1H, 7-H), 7.17 (d, *J* = 2.5 Hz, 1H, 1-H), 7.00 (dd, *J* = 8.2, 2.5 Hz, 1H, 4-H), 3.85 (s, 3H, OCH_3).

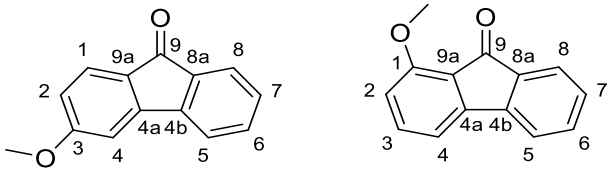
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 194.1 (C-9), 161.5 (C-2), 145.4 (C-4b), 137.4 (C-4a), 136.5 (C-9a), 135.4 (C-6), 134.9 (C-8a), 128.4 (C-7), 124.6 (C-8), 122.0 (C-4), 120.5 (C-3), 120.2 (C-5), 109.9 (C-1), 56.3 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2998, 2972, 2837, 1717, 1604, 1491, 1465, 1289, 1233, 1038, 953, 927, 735.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{10}O_2^{\bullet+}$ 210.0681; found 210.0674.

Literature known compound.[180]

3-Methoxy-9*H*-fluoren-9-one (1d) and **1-methoxy-9*H*-fluoren-9-one (1k)**



$C_{14}H_{10}O_2$

M = 210.2320 g/mol

These compounds were prepared in accordance with **General procedure A1** from

a) secondary amine **173d** (105 mg, 0.462 mmol) and aqueous TBHP (70%, 0.180 mL, 1.80 mmol). Purification by FCC afforded the product **1d** as a yellow solid (27.0 mg, 0.128 mmol, 28%).
b) primary amine **184k** (177 mg, 0.830 mmol) and aqueous TBHP (70%, 0.460 mL, 3.32 mmol). Purification by FCC afforded the product **1k** as a yellow solid (73.0 mg, 0.347 mmol, 42%). The compound **1k** was accompanied by its regioisomer **1d**, obtained as a yellow solid (26.0 mg, 0.124 mmol, 15%).

3-Methoxy-9*H*-fluoren-9-one (**1d**):

R_f: 0.32 (hexanes/EtOAc 4:1).

M.p.: 93 - 95 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.61 – 7.56 (m, 2H, 1-H and 8-H), 7.55 – 7.52 (m, 1H, 5-H), 7.49 (td, *J* = 7.3, 1.2 Hz, 1H, 6-H), 7.31 (td, *J* = 7.3, 1.2 Hz, 1H, 7-H), 7.08 (d, *J* = 2.3 Hz, 1H, 4-H), 6.77 (dd, *J* = 8.3, 2.3 Hz, 1H, 2-H), 3.91 (s, 3H, OCH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 192.7 (C-9), 166.1 (C-3), 147.6 (C-4a), 143.9 (C-4b), 135.9 (C-8a), 134.7 (C-7), 129.9 (C-6), 127.6 (C-9a), 126.5 (C-8), 124.1 (C-1), 120.8 (C-5), 113.7 (C-2), 107.6 (C-4), 56.4 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3060, 2926, 2842, 2362, 2342, 1704, 1608, 1598, 1488, 1440, 1299, 1237, 1182, 1097, 1021, 920, 832, 768, 736.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{10}O_2^{\bullet+}$: 210.0681; found 210.0676.

Literature known compound.[244]

1-Methoxy-9*H*-fluoren-9-one (**1k**):

R_f: 0.29 (hexanes/EtOAc 10:1).

M.p.: 132 – 134 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.58 (ddd, J = 7.3, 1.2, 0.7 Hz, 1H, 8-H), 7.54 (dt, J = 7.4, 0.9 Hz, 1H, 5-H), 7.52 – 7.44 (m, 2H, 3-H and 6-H), 7.31 (td, J = 7.4, 1.1 Hz, 1H, 7-H), 7.17 (dd, J = 7.3, 0.6 Hz, 1H, 4-H), 6.87 (dd, J = 8.5, 0.7 Hz, 1H, 2-H), 3.96 (s, 3H, OCH_3).

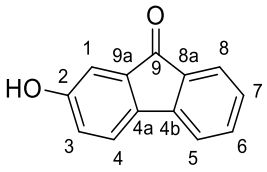
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 191.8 (C-9), 158.7 (C-1), 146.8 (C-4a), 143.6 (C-4b), 137.2 (C-3), 134.9 (C-8a), 134.3 (C-6), 129.6 (C-7), 123.9 (C-8), 120.7 (C-5), 120.4 (C-9a), 113.6 (C-2), 113.3 (C-4), 56.2 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3060, 2923, 2842, 1698, 1607, 1590, 1487, 1454, 1438, 1362, 1292, 1232, 1180, 1152, 1094, 1019, 915, 873, 831, 765, 732, 673.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{10}O_2^{\bullet+}$: 210.0681; found 210.0674.

Literature known compound.[245]

2-Hydroxy-9*H*-fluoren-9-one (1e)



$C_{13}H_8O_2$

M = 196.2050 g/mol

This compound was prepared in accordance with **General procedure B** from 2-bromofluorenone (**284**, 130 mg, 0.500 mmol), $Pd_2(dba)_3$ (18.3 mg, 0.0200 mmol), Me_4*t*ButylXPhos (19.2 mg, 0.0400 mmol) and KOH (56.1 mg, 1.00 mmol). Purification by FCC afforded the product **1e** as an orange solid (75.0 mg, 0.382 mmol, 76%).

R_f: 0.64 (hexanes/EtOAc 2:1).

M.p.: 206 – 207 °C.

^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ (ppm) = 10.05 (1H, s, OH), 7.61 – 7.53 (m, 3H, H_{arom}), 7.52 – 7.49 (m, 2H, H_{arom}), 7.23 (td, J = 7.4, 1.0 Hz, 1H, H_{arom}), 6.97 – 6.91 (m, 2H, H_{arom}).

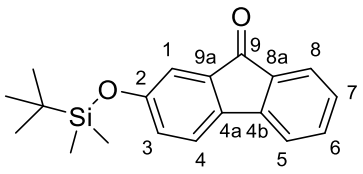
^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ (ppm) = 193.3 (C-9), 158.9 (C-2), 144.8 (C_{arom}), 135.4 (C_{arom}), 135.2 (C_{arom}), 134.7 (C_{arom}), 133.3 (C_{arom}), 127.8 (C_{arom}), 123.8 (C_{arom}), 122.4 (C_{arom}), 121.0 (C_{arom}), 120.0 (C_{arom}), 111.0 (C_{arom}).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3221, 1685, 1600, 1455, 1390, 1333, 1293, 1216, 1136, 852, 819, 762, 738.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{13}H_8O_2^{\bullet+}$: 196.0524; found 196.0517.

Literature known compound.[246]

2-((*tert*-Butyldimethylsilyl)oxy)-9*H*-fluoren-9-one (1f)



$C_{19}H_{22}O_2Si$

M = 310.4680 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184f** (119 mg, 0.380 mmol) and aqueous TBHP (70%, 0.210 mL, 1.52 mmol). Purification by FCC afforded the pure product **1f** as a yellow oil (46.0 mg, 0.148 mmol, 39%) and a product mixture of **1f** and the aldehyde (17.9 mg) in a ratio of approximately 3:1 as determined by ^{1}H NMR. The approximated total yield of product **1f** furnished is therefore 59.4 mg (0,191 mmol, 50%).

R_f: 0.58 (hexanes/EtOAc 10:1).

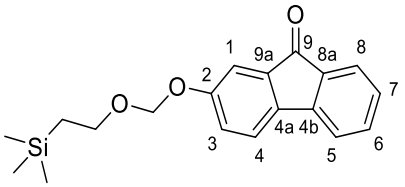
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.57 (dt, *J* = 7.3, 1.0 Hz, 1H, 8-H), 7.47 – 7.44 (m, 2H, 5-H and 6-H), 7.41 (dd, *J* = 8.0, 0.5 Hz, 1H, 4-H), 7.22 (ddd, *J* = 7.3, 5.5, 3.0 Hz, 1H, 7-H), 7.09 (dd, *J* = 2.3, 0.5 Hz, 1H, 1-H), 6.95 (dd, *J* = 8.0, 2.3 Hz, 1H, 3-H), 1.00 (s, 9H, $C(CH_3)_3$), 0.24 (s, 6H, $Si(CH_3)_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 193.8 (C-9), 157.4 (C-2), 145.2 (C-4b), 137.9 (C-4a), 136.4 (C-9a), 135.2 (C-6), 134.8 (C-8a), 128.3 (C-7), 126.0 (C-3), 124.4 (C-8), 121.8 (C-5), 120.1 (C-4), 116.4 (C-1), 25.8 ($C(\underline{C}H_3)_3$), 18.5 ($\underline{C}(CH_3)_3$), -4.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954, 2929, 2886, 2857, 2360, 1715, 1602, 1486, 1472, 1454, 1269, 1238, 1190, 1133, 1076, 1005, 975, 885, 826, 780, 763, 733, 693, 661.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{19}H_{22}O_2Si^{\bullet+}$: 310.1389; found 310.1383.

2-((2-(Trimethylsilyl)ethoxy)methoxy)-9*H*-fluoren-9-one (1g)



$C_{19}H_{22}O_3Si$

M = 326.4670 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184g** (98.9 mg, 0.300 mmol) and aqueous TBHP (70%, 0.166 mL, 1.20 mmol). Attempt at purification by FCC afforded a mixture of product **1g** and the aldehyde as a yellow oil (55.0 mg) in an approximate ratio of 5.25:1 as determined by ^{1}H NMR. The approximated total yield of product **1f** furnished is therefore 45 mg (0.138 mmol, 46%).

R_f: 0.47 (hexanes/EtOAc 10:1).

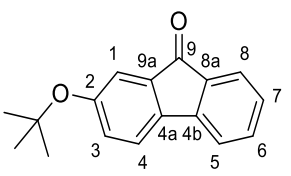
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.61 (dt, J = 7.3, 1.0 Hz, 1H, 1-H), 7.45 – 7.42 (m, 2H, 5-H and 6-H), 7.41 (dd, J = 8.2, 0.5 Hz, 1H, 4-H), 7.34 (dd, J = 2.4, 0.5 Hz, 1H, 1-H), 7.21 (ddd, J = 7.3, 6.5, 2.0 Hz, 1H, 7-H), 7.12 (dd, J = 8.1, 2.4 Hz, 1H, 3-H), 5.25 (s, 2H, OCH_2O), 3.79 – 3.74 m, (2H, $OC\underline{H}_2CH_2$), 1.00 – 0.93 (m, 2H, $OCH_2C\underline{H}_2$), 0.00 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 193.8 (C-9), 158.8 (C-2), 144.9 (C-4b), 137.9 (C-4a), 136.0 (C-9a), 134.9 (C-6), 134.5 (C-8a), 128.2 (C-7), 124.5 (C-8), 122.0 (C-3), 121.4 (C-4), 119.8 (C-5), 112.6 (C-1), 93.1 (OCH_2), 66.6 ($O\underline{C}H_2CH_2$), 18.2 ($OCH_2\underline{C}H_2$), -1.3 ($Si(\underline{C}H_3)_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2952, 2924, 2898, 1716, 1603, 1488, 1456, 1295, 1271, 1235, 1070, 1008, 988, 947, 830, 763, 733.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{19}H_{22}O_3Si^{\bullet+}$: 326.1338; found 326.1327.

2-(*tert*-Butoxy)-9*H*-fluoren-9-one (1h)



$C_{17}H_{16}O_2$

M = 252.313 g/mol

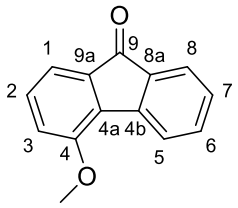
This compound was prepared in accordance with **General procedure A1** from crude amine **184h** (197 mg, 0.770 mmol) and aqueous TBHP (70%, 0.426 mL, 3.08 mmol). Attempt at purification by FCC afforded the crude product **1h** as a yellow oil (35.0 mg, 0.139 mmol, 18% crude yield).

R_f: 0.64 (hexanes/EtOAc 4:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.47 – 7.42 (m, 1H), 7.35 – 7.19 (m, 4H), 7.04 – 6.97 (m, 2H), 1.37 (s, 9H).

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{17}H_{26}O_2^{\bullet+}$: 252.1150; found 252.1154.

4-Methoxy-9*H*-fluoren-9-one (1j)



$C_{14}H_{10}O_2$

M = 210.2320 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184j** (75.0 mg, 0.350 mmol) and aqueous TBHP (70%, 0.194 mL, 1.40 mmol). Purification by FCC afforded the product **1j** as an orange solid (38.0 mg, 0.181 mmol, 52%).

R_f: 0.36 (hexanes/EtOAc 10:1).

M.p.: 100 – 103 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.56 (dt, *J* = 7.3, 1.0 Hz, 1H, 1-H), 7.47 – 7.42 (m, 3H, 3-H and 4-H and 7-H), 7.21 (ddd, *J* = 7.3, 5.9, 2.5 Hz, 1H, 2-H), 7.17 (d, *J* = 2.5 Hz, 1H, 8-H), 7.00 (dd, *J* = 8.2, 2.5 Hz, 1H, 6-H), 3.85 (s, 3H, OCH_3).

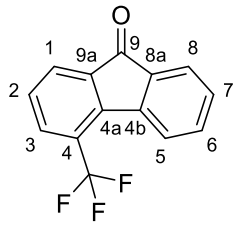
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 194.0 (C-9), 161.5 (C-5), 145.4 (C-4a), 137.4 (C-4b), 136.5 (C-8a or C-9a), 135.4 (C-3), 134.9 (C-8a or C-9a), 128.4 (C-2), 124.6 (C-1), 122.0 (C-4 or C-7), 120.5 (C-6), 120.2 (C-4 or C-7), 109.9 (C-8), 56.3 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3010, 2924, 2854, 1716, 1602, 1490, 1454, 1424, 1298, 1272, 1246, 1200, 1141, 1034, 1017, 964, 863, 834, 761, 728, 212.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{10}O_2^{\bullet+}$: 210.0681; found 210.0674.

Literature known compound.[247]

4-(Trifluoromethyl)-9*H*-fluoren-9-one (1l)



$C_{14}H_7F_3O$

M = 248.2042 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184l** (50.3 mg, 0.200 mmol) and aqueous TBHP (70%, 0.111 mL, 0.800 mmol). Purification by FCC afforded the product **1l** as a yellow solid (14.0 mg, 0.0564 mmol, 28%).

R_f: 0.52 (hexanes/EtOAc 10:1).

M.p.: 122 - 124 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.90 – 7.84 (m, 2H, 2-H and 1-H), 7.80 (dd, *J* = 7.9, 1.0 Hz, 1H, 3-H), 7.73 (dt, *J* = 7.5, 1.0 Hz, 1H, 8-H), 7.58 (td, *J* = 7.7, 1.4 Hz, 1H, 6-H), 7.45 (ddd, *J* = 8.0, 7.3, 0.9 Hz, 1H, 5-H), 7.42 (td, *J* = 7.4, 0.9 Hz, 1H, 7-H).

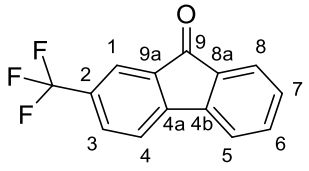
^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 192.6 (C-9), 142.7 (t, *J* = 2.2 Hz, C-4a), 142.0 (C-4b), 136.3 (C-9a), 135.9 (C-6), 134.6 (C-8a), 131.8 (q, *J* = 5.7 Hz, C-3), 130.7 (C-7), 129.7 (C-5), 127.7 (C-1), 125.1 (q, *J* = 5.6 Hz, C-2), 124.8 (C-8), 124.6 (q, *J* = 32.8 Hz, C-4), 124.3 (q, *J* = 272.3, CF_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2923, 2853, 1716, 1607, 1578, 1466, 1424, 1327, 1303, 1258, 1171, 1156, 1114, 1089, 1070, 932, 886, 829, 737, 718.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_7F_3O^{\bullet+}$: 248.0449; found 248.0442.

Literature known compound.[248]

2-(Trifluoromethyl)-9*H*-fluoren-9-one (1m)



$C_{14}H_7F_3O$

M = 248.2042 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184m** (146 mg, 0.580 mmol) and aqueous TBHP (70%, 0.321 mL, 2.32 mmol). Purification by FCC afforded the product **1m** as a yellow solid (26.0 mg, 0.105 mmol, 18%).

R_f: 0.40 (hexanes/EtOAc 10:1).

M.p.: 130 – 132 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.89 – 7.87 (m, 1H, 1-H), 7.80 (ddd, *J* = 7.8, 1.8, 0.9 Hz, 1H, 3-H), 7.72 – 7.68 (m, 2H, 8-H and 4-H), 7.66 (dt, *J* = 7.5, 0.9 Hz, 1H, 5-H), 7.59 (td, *J* = 7.5, 1.2 Hz, 1H, 6-H), 7.41 (td, *J* = 7.5, 1.1 Hz, 1H, 7-H).

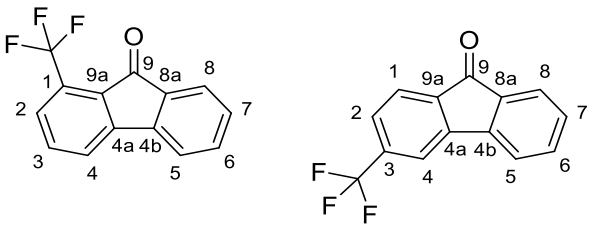
^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 192.3 (C-9), 148.0 (C-4a), 143.5 (C-4b), 135.6 (C-6), 135.0 (C-8a or C-9a), 134.7 (C-8a or C-9a), 132.0 (q, *J* = 3.9 Hz, C-3), 131.4 (q, *J* = 32.8 Hz, C-2), 130.7 (C-7), 124.9 (C-8 or C-4), 124.3 (q, *J* = 272.2 Hz, CF_3), 121.7 (C-5), 121.4 (q, *J* = 3.8 Hz, C-1), 121.1 (C-8 or C-4).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2922, 2853, 1716, 1622, 1606, 1466, 1458, 1325, 1266, 1146, 1107, 1054, 907, 849, 815, 769, 736, 656.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_7F_3O^{\bullet+}$: 248.0449; found 248.0443.

Literature known compound.[249]

1-(Trifluoromethyl)-9*H*-fluoren-9-one (1n1) and **3-(trifluoromethyl)-9*H*-fluoren-9-one (1n2)**



$C_{14}H_7F_3O$

M = 248.2042 g/mol

These compounds were prepared in accordance with **General procedure A1** from amine **184n** (130 mg, 0.516 mmol) and aqueous TBHP (70%, 0.200 mL, 2.06 mmol). Purification by

FCC afforded the product **1n1** as a yellow solid (40.0 mg, 0.161 mmol, 31%). The compound **1n1** was accompanied by its regioisomer **1n2**, obtained as a yellow solid (35.0 mg, 0.141 mmol, 27%).

1-(Trifluoromethyl)-9*H*-fluoren-9-one (**1n1**):

R_f: 0.57 (hexanes/EtOAc 10:1).

M.p.: 124 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.79 (d, J = 7.4 Hz, 1H, 4-H), 7.67 (dt, J = 7.4, 1.0 Hz, 1H, 8-H), 7.65 – 7.59 (m, 2H, 3-H and 5-H), 7.58 – 7.54 (m, 2H, 2-H and 6-H), 7.38 (td, J = 7.4, 1.1 Hz, 1H, 7-H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 190.3 (C-9), 146.9 (C-4a), 143.3 (C-4b), 135.4 (C-6), 135.0 (C-3), 133.7 (C-8a), 131.2 (C-9a), 130.4 (C-7), 127.6 (q, J = 35.2 Hz, C-1), 126.3 (q, J = 5.7 Hz, C-2), 124.9 (C-8), 124.2 (C-4), 123.5 (q, J = 274.6 Hz, CF_3), 120.9 (C-5).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1718, 1608, 1592, 1318, 1294, 1267, 1172, 1136, 1116, 1108, 1083, 1065, 1038, 918, 800, 754, 717, 677.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_7F_3O^{\bullet+}$: 248.0449; found 248.0444.

Literature known compound.[248]

3-(Trifluoromethyl)-9*H*-fluoren-9-one (**1n2**):

R_f: 0.31 (hexanes/EtOAc 10:1).

M.p.: 133 – 135 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.80 (t, J = 0.8 Hz, 1H, 4-H), 7.74 (dt, J = 7.8, 0.8 Hz, 1H, 1-H), 7.69 (dt, J = 7.4, 1.0 Hz, 1H, 8-H), 7.64 (dt, J = 7.5, 1.0 Hz, 1H, 5-H), 7.60 (ddd, J = 7.7, 1.6, 0.8 Hz, 1H, 2-H), 7.58 (td, J = 7.4, 1.1 Hz, 1H, 6-H), 7.39 (td, J = 7.4, 1.1 Hz, 1H, 7-H).

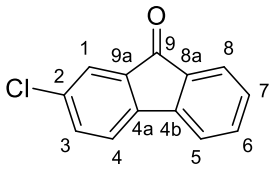
^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 192.7 (C-9), 145.4 (C-4a), 143.6 (C-4b), 137.2 (C-9a), 136.3 (q, J = 32.6 Hz, C-3), 135.7 (C-6), 134.4 (C-8a), 130.4 (C-7), 126.7 (q, J = 4.1 Hz, C-2), 124.9 (C-1), 124.6 (C-8), 124.1 (q, J = 273.2 Hz, CF_3), 121.3 (C-5), 117.7 (q, J = 3.8 Hz, C-4).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3058, 2922, 1712, 1624, 1600, 1478, 1423, 1319, 1303, 1268, 1165, 1115, 1053, 919, 844, 762, 744, 682, 663.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_7F_3O^{\bullet+}$: 248.0449; found 248.0443.

Literature known compound.[250]

2-Chloro-9*H*-fluoren-9-one (1o)



$C_{13}H_7ClO$

M = 214.6480 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184o** (107 mg, 0.490 mmol) and aqueous TBHP (70%, 0.271 mL, 1.96 mmol). Purification by FCC afforded the product **1o** as a yellow solid (27.0 mg, 0.126 mmol, 26%).

R_f: 0.49 (hexanes/EtOAc 10:1).

M.p.: 119 – 121 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.64 (dt, *J* = 7.4, 1.0 Hz, 1H, 8-H), 7.58 (dd, *J* = 1.9, 0.7 Hz, 1H, 1-H), 7.55 – 7.52 (m, 2H, 5-H and 6-H), 7.50 (d, *J* = 0.7 Hz, 1H, 3-H), 7.48 (d, *J* = 1.8 Hz, 1H, 4-H), 7.33 (ddd, *J* = 7.3, 6.6, 2.0 Hz, 1H, 7-H).

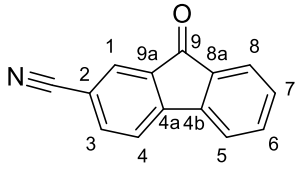
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 192.2 (C-9), 143.6 (C-4b), 142.6 (C-4a), 135.7 (C-2 or C-9a), 135.1 (C-6), 134.9 (C-8a), 134.2 (C-3), 133.9 (C-2 or C-9a), 129.3 (C-7), 124.3 (C-1 and C-8), 121.6 (C-4), 120.6 (C-5).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3049, 2923, 2853, 2360, 2341, 1706, 1615, 1599, 1449, 1417, 1299, 1258, 1190, 1113, 1063, 947, 879, 832, 800, 759, 728, 66.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{13}H_7{}^{35}ClO^{\bullet+}$: 214.0185; found 214.0179.

Literature known compound.[242]

2-Cyano-9*H*-fluoren-9-one (1p)



$C_{14}H_7NO$

M = 205.2160 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184p** (154 mg, 0.740 mmol) and aqueous TBHP (70%, 0.410 mL, 2.96 mmol). Purification by FCC afforded the product **1p** as a yellow solid (20.0 mg, 0.0974 mmol, 13%).

R_f: 0.35 (hexanes/EtOAc 4:1).

M.p.: 170 – 171 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.88 (dd, *J* = 1.5, 0.7 Hz, 1H, 1-H), 7.82 (dd, *J* = 7.7, 1.5 Hz, 1H, 3-H), 7.72 (dt, *J* = 7.4, 1.0 Hz, 1H, 8-H), 7.70 – 7.65 (m, 2H, 4-H and 5-H), 7.60 (td, *J* = 7.5, 1.2 Hz, 1H, 6-H), 7.44 (td, *J* = 7.4, 1.1 Hz, 1H, 7-H).

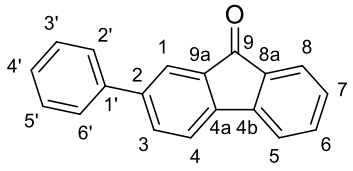
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 191.7 (C-9), 148.4 (C-4a), 143.2 (C-4b), 139.0 (C-3), 135.7 (C-6), 134.9 (C-9a), 134.6 (C-8a), 131.1 (C-7), 127.7 (C-1), 125.0 (C-8), 122.0 (C-5), 121.5 (C-4), 118.5 (CN), 113.0 (C-2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3089, 3049, 2922, 2853, 2233, 1713, 1604, 1457, 1292, 1178, 1105, 963, 928, 854, 765, 725, 689.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_7NO^{\bullet+}$: 205.0528; found 205.0520.

Literature known compound.[248]

2-Phenyl-9*H*-fluoren-9-one (1q)



$C_{19}H_{12}O$

M = 256.3040 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184q** (207 mg, 0.800 mmol) and aqueous TBHP (70%, 0.310 mL, 3.20 mmol). Purification by FCC afforded the product **1q** a yellow solid (105 mg, 0.410 mmol, 51%).

R_f: 0.44 (hexanes/EtOAc 10:1).

M.p.: 140 – 141 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.88 (d, *J* = 1.7 Hz, 1H, 1-H), 7.76 (dd, *J* = 7.8, 1.8 Hz, 1H, 3-H), 7.67 – 7.61 (m, 4H, 8-H, and H_{arom}), 7.59 (dt, *J* = 7.7, 1.0 Hz, 1H, H_{arom}), 7.53 (td, *J* =

7.5, 1.2 Hz, 1H, 6-H), 7.50 – 7.44 (m, 2H, 3'-H and 5'-H), 7.42 – 7.36 (m, 1H, H_{arom}), 7.32 (td, *J* = 7.4, 1.1 Hz, 1H, H_{arom}).

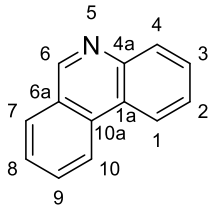
^{13}C NMR (101 MHz, CD_2Cl_2): *δ* (ppm) = 193.9 (C-9), 144.6 (C-5), 143.6 (C-1), 142.6 (C_{arom}), 140.2 (C-1'), 135.3 (C_{arom}), 135.2 (C-6), 134.9 (C_{arom}), 133.6 (C-3), 129.4 (C_{arom}), 129.3 (C-3' and C-5'), 128.3 (C_{arom}), 127.2 (C_{arom}), 124.5 (C_{arom}), 123.0 (C-8), 121.2 (C_{arom}), 120.9 (C_{arom}).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3055, 2922, 2853, 1710, 1617, 1600, 1455, 1422, 1399, 1188, 1146, 1110, 942, 847, 756, 736, 698.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{19}H_{12}O^{\bullet+}$: 256.0888; found 256.0883.

Literature known compound.[251]

Phenanthridine (1r)



$C_{13}H_9N$

M = 179.2220 g/mol

This compound was prepared accidentally in accordance with **General procedure A1** from amine **184r** (97.3 mg, 0.405 mmol) and aqueous TBHP (70%, 0.224 mL, 1.62 mmol). Purification by FCC gave the product **1r** as a white solid (26.0 mg, 0.145 mmol, 36%).

R_f: 0.30 (hexanes/EtOAc 4:1).

M.p.: 103 – 105 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): *δ* (ppm) = 9.28 (s, 1H, 6-H), 8.65 (dd, *J* = 8.4, 1.1 Hz, 1H, 10-H), 8.62 (dd, *J* = 8.0, 1.6 Hz, 1H, 1-H), 8.17 (dd, *J* = 7.9, 1.5 Hz, 1H, 4-H), 8.08 (dt, *J* = 7.9, 1.0 Hz, 1H, 7-H), 7.89 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H, 9-H), 7.79 – 7.68 (m, 3H, 2-H and 3-H and 8-H).

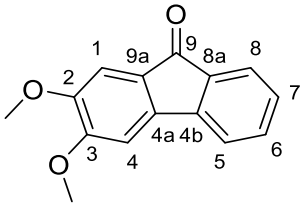
^{13}C NMR (101 MHz, CD_2Cl_2): *δ* (ppm) = 154.0 (C-6), 145.0 (C-4a), 132.8 (C-10a), 131.4 (C-9), 130.5 (C-4), 129.1 (C-2 or C-3 or C-8), 129.0 (C-7), 127.9 (C-2 or C-3 or C-8), 127.4 (C-2 or C-3 or C-8), 126.9 (C-6a), 124.4 (C-1a), 122.7 (C-1), 122.3 (C-10).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2922, 2852, 1725, 1615, 1587, 1574, 1525, 1489, 1457, 1443, 1401, 1342, 1288, 1243, 1193, 1145, 1134, 1033, 969, 890, 861, 773, 746, 720.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{13}H_9N^{\bullet+}$: 179.0735; found 179.0727.

Literature known compound.[252]

2,3-Dimethoxy-9*H*-fluoren-9-one (1s1)



$C_{15}H_{12}O_3$

M = 240.2580 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184s** (122 mg, 0.500 mmol) and aqueous TBHP (70%, 0.277 mL, 2.00 mmol). Purification by FCC afforded the product **1s1** as an orange solid (42.0 mg, 0.175 mmol, 35%).

R_f: 0.23 (hexanes/EtOAc 4:1).

M.p.: 158 – 160 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.50 (dt, *J* = 7.3, 1.0 Hz, 1H, 8-H), 7.42 (td, *J* = 7.3, 1.1 Hz, 1H, 6-H), 7.41 – 7.38 (m, 1H, 5-H), 7.20 (td, *J* = 7.3, 1.3 Hz, 1H, 7-H), 7.15 (s, 1H, 1-H), 7.03 (s, 1H, 4-H), 3.97 (s, 3H, 2-OCH_3 or 3-OCH_3), 3.88 (s, 3H, 2-OCH_3 or 3-OCH_3).

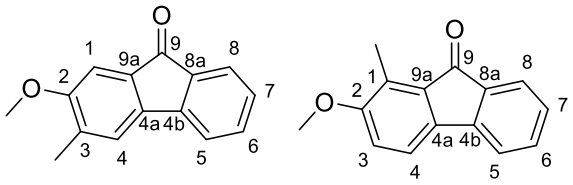
^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 193.3 (C-9), 155.4 (C-3), 150.6 (C-2), 144.6 (C-4b), 139.9 (C-4a), 135.4 (C-8a), 134.8 (C-6), 128.7 (C-7), 127.6 (C-9a), 123.9 (C-8), 119.7 (C-5), 107.6 (C-1), 104.2 (C-4), 56.8 (2-OCH_3 or 3-OCH_3), 56.7 (2-OCH_3 or 3-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1703, 1587, 1499, 1461, 1413, 1365, 1324, 1287, 1262, 1242, 1208, 1160, 1113, 1023, 857, 763, 735, 713.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{12}O_3^{\bullet+}$: 240.0786; found 240.0784.

Literature known compound.[166]

2-Methoxy-3-methyl-9*H*-fluoren-9-one (1t1) and **2-methoxy-1-methyl-9*H*-fluoren-9-one (1t2)**



$C_{15}H_{12}O_2$

M = 224.2590 g/mol

These compounds were prepared in accordance with **General procedure A1** from amine **184t** (111 mg, 0.490 mmol) and aqueous TBHP (70%, 0.271 mL, 1.96 mmol). Purification by FCC afforded the product **1t1** as a yellow solid (27.0 mg, 0.120 mmol, 25%). The compound **1t1** was accompanied by its regioisomer **1t2**, obtained as a yellow solid (36.1 mg, 0.156 mmol, 32%).

2-Methoxy-3-methyl-9*H*-fluoren-9-one (**1t1**):

R_f: 0.44 (hexanes/EtOAc 10:1).

M.p.: 144 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.52 (dt, J = 7.3, 1.0 Hz, 1H, C-8), 7.45 – 7.37 (m, 2H, 5-H and 6-H), 7.31 (s, 1H, 4-H), 7.19 (td, J = 7.1, 1.5 Hz, 1H, 7-H), 7.12 (s, 1H, 1-H), 3.88 (s, 3H, OCH_3), 2.27 (d, J = 0.8 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 194.0 (C-9), 159.3 (C-2), 145.3 (C-4b), 137.5 (C-4a), 135.0 (C-6), 134.9 (C-8a), 134.4 (C-3), 134.0 (C-9a), 128.1 (C-7), 124.1 (C-8), 123.1 (C-4), 119.8 (C-5), 106.0 (C-1), 56.1 (C-OCH_3), 17.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2922, 2853, 1706, 1597, 1458, 1378, 1364, 1300, 1261, 1197, 1110, 1077, 1041, 1018, 880, 860, 765, 738, 697.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{12}O_2$ 224.0837; found 224.0832.

2-Methoxy-1-methyl-9*H*-fluoren-9-one (**1t2**):

R_f: 0.46 (hexanes/EtOAc 10:1).

M.p.: 129 °C.

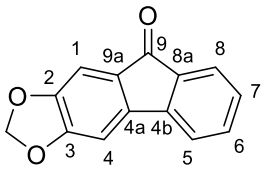
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.55 (dt, *J* = 7.4, 1.0 Hz, 1H, 8-H), 7.46 – 7.43 (m, 2H, 5-H and 6-H), 7.32 (dd, *J* = 8.1, 1H, 4-H), 7.24 – 7.17 (m, 1H, 7-H), 6.87 (d, *J* = 8.1 Hz, 1H, 3-H), 3.86 (s, 3H, OCH_3), 2.50 (s, 3H, CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 195.3 (C-9), 159.8 (C-2), 144.6 (C-4b), 136.6 (C-4a), 135.1 (C-8a), 134.9 (C-6), 132.6 (C-9a), 129.8 (C-1), 128.0 (C-7), 124.0 (C-8), 119.8 (C-5), 118.7 (C-4), 114.2 (C-3), 56.4 (OCH_3), 10.2 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2957, 2922, 2853, 1693, 1598, 1460, 1436, 1376, 1297, 1262, 1230, 1190, 1111, 1067, 1014, 932, 820, 795, 762, 740, 719, 680.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{12}O_2^{\bullet+}$: 224.0837; found 224.0832.

9*H*-Fluoreno[2,3-*d*][1,3]dioxol-9-one (1u1)



$C_{14}H_8O_3$

M = 224.2150 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184u** (107 mg, 0.470 mmol) and aqueous TBHP (70%, 0.260 mL, 1.88 mmol). Purification by FCC afforded the product **1u1** an orange solid (8.50 mg, 0.0379 mmol, 8%).

R_f: 0.30 (hexanes/EtOAc 10:1).

M.p.: 146 – 148 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.50 (dt, *J* = 7.3, 1.0 Hz, 1H, 8-H), 7.43 (td, *J* = 7.4, 1.2 Hz, 1H, 6-H), 7.36 (dt, *J* = 7.3, 0.9 Hz, 1H, 5-H), 7.22 (td, *J* = 7.4, 1.1 Hz, 1H, 7-H), 7.05 (d, *J* = 0.5 Hz, 1H, 1-H), 7.00 (d, *J* = 0.5 Hz, 1H, 4-H), 6.06 (s, 2H, OCH_2O).

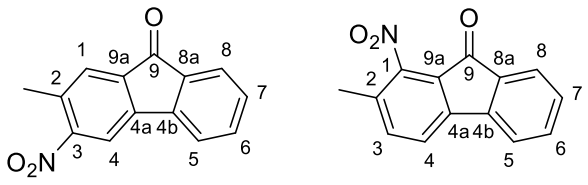
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 192.4 (C-9), 153.8 (C-4), 149.0 (C-2), 144.0 (C-4b), 142.0 (C-4a), 135.1 (C-8a), 134.7 (C-6), 129.0 (C-9a), 128.7 (C-7), 123.8 (C-8), 119.7 (C-4), 105.1 (C-1), 102.9 (OCH_2O), 102.1 (C-5).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2922, 2853, 1699, 1605, 1591, 1477, 1456, 1366, 1341, 1259, 1220, 1179, 1024, 926, 888, 866, 759, 728, 702.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_8O_3^{\bullet+}$: 224.0473; found 224.0467.

Literature known compound.[253]

2-Methyl-3-nitro-9*H*-fluoren-9-one (1v1) and **2-methyl-1-nitro-9*H*-fluoren-9-one (1v2)**



$C_{14}H_9NO_3$

M = 239.2300 g/mol

These compounds were prepared in accordance with **General procedure A1** from amine **184v** (124 mg, 0.510 mmol) and aqueous TBHP (70%, 0.282 mL, 2.04 mmol). Purification by FCC afforded the product **1v1** as a yellow solid (23.0 mg, 0.0961 mmol, 19%). The compound **1v1** was accompanied by its regioisomer **1v2**, obtained as a yellow solid (15.0 mg, 0.0627 mmol, 12%).

2-Methyl-3-nitro-9*H*-fluoren-9-one (**1v1**):

R_f: 0.38 (hexanes/EtOAc 4:1).

M.p.: 209 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 8.02 (s, 1H, 4-H), 7.69 (dt, *J* = 7.4, 1.0 Hz, 1H, 8-H), 7.63 – 7.56 (m, 3H, 1-H and 5-H and 6-H), 7.39 (td, *J* = 7.2, 1.7 Hz, 1H, 7-H), 2.58 (s, 3H, CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 192.2 (C-9), 153.6 (C-3), 143.3 (C-4a or C-4b), 143.1 (C-4a or C-4b), 137.1 (C-9a), 136.0 (C-6), 135.2 (C-2), 134.5 (C-8a), 130.4 (C-7), 128.5 (C-1), 124.9 (C-8), 121.5 (C-5), 116.8 (C-4), 20.5 (CH_3).

IR (ATR): 2922, 2853, 1714, 1602, 1519, 1449, 1339, 1297, 1179, 1120, 880, 816, 755, 734, 721.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_9NO_3^{\bullet+}$: 239.0582; found 239.0575.

2-Methyl-1-nitro-9*H*-fluoren-9-one (**1v2**):

R_f: 0.30 (hexanes/EtOAc 4:1).

M.p.: 199 °C.

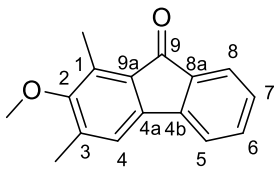
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.64 (dt, J = 7.3, 1.0 Hz, 1H, 8-H), 7.60 – 7.52 (m, 4-H, 3H, 5-H and 6-H), 7.47 (dq, J = 7.6, 0.8 Hz, 1H, 3-H), 7.36 (ddd, J = 7.4, 6.6, 1.9 Hz, 1H, 7-H), 2.30 (d, J = 0.7 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 189.1 (C-9), 143.8 (C-4a), 143.2 (C-4b), 138.2 (C-3), 135.7 (C-6), 133.8 (C-8a), 130.3 (C-7), 130.2 (C-1), 125.2 (C-8), 124.1 (C-2 and C-9a), 122.4 (C-4), 121.2 (C-5), 16.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2922, 2853, 1709, 1618, 1604, 1528, 1457, 1377, 1354, 1294, 1268, 1183, 1154, 968, 836, 812, 760, 750, 692.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{14}H_9NO_3^{\bullet+}$: 239.0582; found 239.0574.

2-Methoxy-1,3-dimethyl-9*H*-fluoren-9-one (1w)



$C_{16}H_{14}O_2$

M = 238.2860 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184w** (106 mg, 0.440 mmol) and aqueous TBHP (70%, 0.244 mL, 1.76 mmol). Purification by FCC afforded the product **1w** as a yellow solid (65.0 mg, 0.273 mmol, 62%).

R_f: 0.49 (hexanes/EtOAc 10:1).

M.p.: 83 °C.

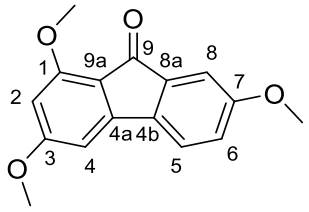
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.54 (dt, J = 7.3, 1.0 Hz, 1H, 8-H), 7.46 – 7.45 (m, 1H, 6-H), 7.44 (t, J = 1.0 Hz, 1H, 5-H), 7.26 – 7.22 (m, 1H, 7-H), 7.22 (d, J = 0.7 Hz, 1H, 4-H), 3.72 (s, 3H, OCH_3), 2.53 (s, 3H, 1-CH_3), 2.33 (d, J = 0.7 Hz, 3H, 3-CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 194.3 (C-9), 158.3 (C-2), 143.6 (C-4b), 140.2 (C-4a), 137.6 (C-3), 135.0 (C-8a), 134.2 (C-6), 133.0 (C-1), 130.6 (C-9a), 128.2 (C-7), 123.5 (C-8), 120.5 (C-4), 119.6 (C-5), 60.0 (OCH_3), 16.8 (3-CH_3), 10.6 (1-CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2922, 2853, 1700, 1602, 1454, 1403, 1374, 1296, 1230, 1197, 1128, 1078, 1000, 917, 887, 862, 760, 746, 716, 701.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{16}H_{14}O_2^{\bullet+}$: 238.0994; found 238.0995.

1,3,7-Trimethoxy-9*H*-fluoren-9-one (1x)



$C_{16}H_{14}O_4$

M = 270.2840 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **184x** (136 mg, 0.499 mmol) and aqueous TBHP (70%, 0.276 mL, 2.00 mmol). Purification by FCC afforded the product **1x** as a yellow solid (70.2 mg, 0.259 mmol, 52%).

R_f: 0.23 (hexanes/EtOAc 2:1).

M.p.: 174 °C.

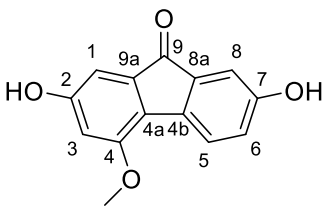
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.38 (d, J = 8.2 Hz, 1H, 5-H), 7.10 (d, J = 2.4 Hz, 1H, 8-H), 6.94 (dd, J = 8.2, 2.4 Hz, 1H, 6-H), 6.62 (d, J = 1.9 Hz, 1H, 4-H), 6.22 (d, J = 1.9 Hz, 1H, 2-H), 3.92 (s, 3H, 1-OCH_3), 3.90 (s, 3H, 3-OCH_3), 3.84 (s, 3H, 7-OCH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 190.1 (C-9), 168.0 (C-3), 161.7 (C-7), 160.5 (C-1), 149.2 (C-4a or C-8a), 138.0 (C-4a or C-8a), 135.0 (C-4b), 121.5 (C-5), 118.9 (C-6), 114.3 (C-9a), 108.9 (C-8), 99.5 (C-4), 97.2 (C-2), 56.3 (1-OCH_3 or 3-OCH_3 or 7-OCH_3), 56.2 (1-OCH_3 or 3-OCH_3 or 7-OCH_3), 56.1 (1-OCH_3 or 3-OCH_3 or 7-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1696, 1595, 1430, 1297, 1207, 1015, 936, 824, 788.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{16}H_{14}O_4^{\bullet+}$: 270.0892; found 270.0887.

Nobilone (8)



$C_{14}H_{10}O_4$

M = 242.2300 g/mol

A solution of crude ketone **209** (777 mg, 1.65 mmol), Olah's reagent (pyridine·HF, 0.650 mL, 7.26 mmol) and pyridine (0.610 mL, 7.59 mmol) in EtOAc (20 mL) was stirred at room temperature overnight. The reaction was quenched with methoxytrimethylsilane (7.93 mL, 57.8 mmol) and stirred for 40 min. The solvent was evaporated *in vacuo*. Purification by FCC afforded the product (**8**) as a red solid (275 mg, 1.14 mmol, 58% over two steps).

R_f: 0.48 (hexanes/EtOAc 2:1).

M.p.: 263 °C.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 9.83 (s, 2H, OH), 7.37 (d, *J* = 8.0 Hz, 1H, 5-H), 6.87 (d, *J* = 2.3 Hz, 1H, 8-H), 6.82 (dd, *J* = 8.0, 2.5 Hz, 1H, 6-H), 6.59 – 6.54 (m, 2H, 3-H and 1-H), 3.85 (s, 3H, OCH_3).

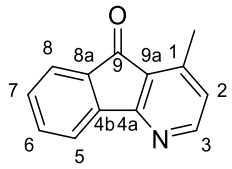
^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 193.6 (C-9), 159.4 (C-2), 156.8 (C-7), 155.2 (C-4), 135.8 (C-9a), 135.0 (C-4b), 134.5 (C-8a), 123.5 (C-5), 122.2 (C-4a'), 120.8 (C-6), 111.3 (C-8), 105.4 (C-3), 103.5 (C-1), 55.6 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3295, 2922, 2852, 1715, 1670, 1599, 1463, 1444, 1313, 1235, 1196, 1155, 1131, 1064, 1027, 959, 908, 880, 832, 790, 779.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{10}O_4^{\bullet+}$: 242.0579; found 242.0566.

Literature known compound.[20]

Onychine (86)



$C_{13}H_9NO$

M = 195.2210 g/mol

This compound was prepared in accordance with **General procedure A2** from pyridinemethanol **274** (99.6 mg, 0.500 mmol) and $TBHP_{dec}$ (5.5 M, 0.727 mL, 4.00 mmol). Purification by FCC afforded the product **86** as a yellow solid (54.0 mg, 0.277 mmol, 55%).

R_f: 0.25 (hexanes/EtOAc 4:1).

M.p.: 132 – 134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.42 (d, J = 5.3 Hz, 1H, 3-H), 7.85 – 7.82 (m, 1H, 5-H), 7.69 (dd, J = 7.3, 1.0 Hz, 1H, 8-H), 7.58 (td, J = 7.5, 1.1 Hz, 1H, 6-H), 7.42 (td, J = 7.5, 1.0 Hz, 1H, 7-H), 6.96 (d, J = 5.4 Hz, 1H, 2-H), 2.63 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 193.4 (C-9), 165.4 (C-4a), 153.0 (C-3), 147.7 (C-1), 143.3 (C-4b), 135.2 (C-6), 135.1 (C-8a), 131.0 (C-7), 126.1 (C-9a), 126.0 (C-2), 123.9 (C-8), 120.9 (C-5), 17.5 (CH_3) ppm.

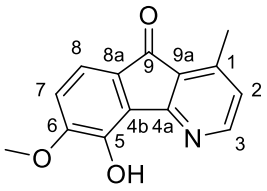
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1702, 1595, 1565, 920, 878, 830, 755.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{13}H_9NO^{\bullet+}$: 195.0684; found 195.0681.

HPLC purity (Method 1b): >95% (210 nm), >95% (254 nm).

Literature known compound.[135]

Isoursuline (90)



$C_{14}H_{11}NO_3$

M = 241.2460 g/mol

This compound was prepared in accordance with **General procedure B** from azafluorenone **290** (122 mg, 0.400 mmol), $Pd_2(dba)_3$ (14.7 mg, 0.0160 mmol), Me_4*t*ButylXPhos (15.4 mg, 0.0320 mmol) and KOH (89.8 mg, 1.60 mmol). Purification by FCC afforded the product **90** as an orange-brown solid (44.0 mg, 0.182 mmol, 46%).

R_f: 0.33 (hexanes/EtOAc 2:1 + 1% AcOH).

M.p.: >240 °C (decomposition).

^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ (ppm) = 9.24 (s, 1H, OH), 8.42 (d, J = 5.4 Hz, 1H, 3-H), 7.21 (d, J = 7.9 Hz, 1H, 8-H), 7.11 (d, J = 5.3 Hz, 1H, 2-H), 6.99 (d, J = 8.0 Hz, 1H, 7-H), 3.91 (s, 3H, OCH_3), 2.54 (s, 3H, CH_3).

^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ (ppm) = 191.03 (C-9), 164.40 (C-4a), 154.49 (C-6), 152.16 (C-3), 146.66 (C-1), 142.69 (C-5), 127.43 (C-8a), 125.66 (C-9a), 125.42 (C-4b), 125.01 (C-2), 116.82 (C-8), 112.59 (C-7), 56.34 (OCH_3), 16.68 (CH_3).

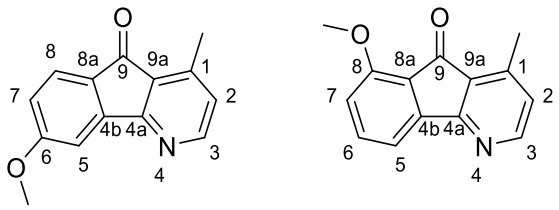
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3334, 1701, 1572, 1513, 1481, 1378, 1262, 1237, 1174, 1073, 996, 880, 838, 797.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}NO_3^{\bullet+}$ 241.0739; found 241.0732.

HPLC purity (Method 1d): >95% (210 nm), >95% (254 nm).

Literature known compound.[101]

6-Methoxyonychine (91) and **8-methoxyonychine (164)**



$C_{14}H_{11}NO_2$

M = 225.2470 g/mol

This compound was prepared in accordance with **General procedure C** from ester **159** (1.36 g, 5.00 mmol) and PPA (4.00 g). Purification by FCC afforded the product (**91**, 205 mg, 0.910 mmol, 18%) as a yellow solid. The compound **91** was accompanied by its regioisomer **164**, obtained as a yellow solid (45.0 mg, 0.200 mmol, 4%).

6-Methoxyonychine (**91**):

R_f: 0.19 (hexanes/EtOAc 4:1).

M.p.: 128 – 130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.39 (d, *J* = 5.3 Hz, 1H, 3-H), 7.64 (d, *J* = 8.3 Hz, 1H, 8-H), 7.35 (d, *J* = 2.3 Hz, 1H, 5-H), 6.96 (dd, *J* = 5.3, 0.8 Hz, 1H, 2-H), 6.87 (dd, *J* = 8.3, 2.3 Hz, 1H, 7-H), 3.94 (s, 3H, OCH_3), 2.63 (d, *J* = 0.7 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 192.1 (C-9), 165.8 (C-6), 164.4 (C-4a), 152.4 (C-3), 147.2 (C-1), 146.1 (C-4b), 128.0 (C-8a), 127.2 (C-9a), 126.3 (C-2), 125.9 (C-8), 116.6 (C-7), 106.0 (C-5), 56.1 (OCH_3), 17.3 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3223, 2940, 2840, 1700, 1586, 1563, 1499, 1453, 1434, 1268, 1208, 1176, 1160, 1045, 958, 810.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}NO_2^{\bullet+}$: 225.0790; found: 225.0783.

HPLC purity (Method 1b): 95% (210 nm), >95% (254 nm).

Literature known compounds.[199]

8-Methoxyonychine (**164**):

R_f: 0.36 (hexanes/EtOAc 1:1).

M.p.: 155 – 156 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.39 (d, J = 5.3 Hz, 1H, 3-H), 7.54 (dd, J = 8.4, 7.3 Hz, 1H, 6-H), 7.45 (dd, J = 7.3, 0.7 Hz, 1H, 5-H), 6.96 – 6.94 (m, 2H, 2-H and 7-H), 3.99 (s, 3H, OCH_3), 2.62 (d, J = 0.7 Hz, 3H, CH_3).

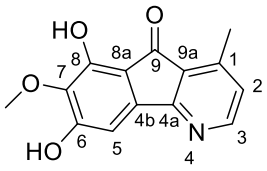
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 191.5 (C-9), 164.2 (C-4a), 158.1 (C-8), 152.4 (C-3), 147.4 (C-1), 145.2 (C-4b), 137.3 (C-6), 126.2 (C-2), 126.2 (C-9a), 120.9 (C-8a), 114.8 (C-7), 113.4 (C-5), 56.1 (OCH_3), 17.3 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2923, 1701, 1614, 1568, 1472, 1362, 1263, 1263, 1217, 1101, 1012, 842.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}NO_2^{\bullet+}$: 25.0790; found: 225.0781.

Literature known compound.[199]

6,8-Dihydroxy-7-methoxyonychine (92)



$C_{14}H_{11}NO_4$

M = 257.2450 g/mol

This compound was prepared in accordance with **General procedure B** from azafluorenone **294** (146 mg, 0.380 mmol), $Pd_2(dba)_3$ (27.8 mg, 0.0304 mmol), Me_4*t*ButylXPhos (29.2 mg, 0.0608 mmol) and KOH (128 mg, 2.28 mmol). Purification by FCC afforded the desired product **92** as a yellow solid (23 mg, 0.0894 mmol, 23%) and azafluorenone **97** as a yellow-orange solid (58.0 mg, 0.240 mmol, 63%).

R_f: 0.36 (hexanes/EtOAc 1:1 + 1% AcOH).

M.p.: 246 – 247 °C (decomposition).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2922, 1668, 1618, 1602, 1566, 1504, 1410, 1328, 1246, 1174, 1152, 1026, 968, 883, 804.

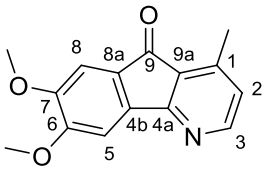
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 10.61 (s, 1H, 6-OH), 9.93 (s, 1H, 8-OH), 8.35 (d, *J* = 5.3 Hz, 1H, 3-H), 7.15 – 7.01 (m, 1H, 2-H), 6.82 (s, 1H, 5-H), 3.72 (s, 3H, OCH_3).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): 189.6 (C-9), 162.7 (C-4a), 157.2 (C-6), 151.8 (C-3), 151.0 (C-8), 145.4 (C-1), 139.1 (C-4b), 137.3 (C-7), 126.3 (C-9a), 125.6 (C-2), 112.3 (C-8a), 101.8 (C-5), 60.2 (OCH_3), 16.3 (CH_3).

HRMS (ESI): *m/z* = $[M+H]^+$ calcd for $C_{14}H_{11}NO_4^+$: 258.0761: found 258.0763.

HPLC purity (Method 3b): >95% (210 nm), >95% (254 nm).

Polyfothine (93)



$C_{15}H_{13}NO_3$

M = 255.2730 g/mol

Bispinacol diborane (33.0 mg, 0.130 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (7.13 mg, 0.00975 mmol, 15mol%) and KOAc (19.1 mg, 0.195 mmol) were added to a solution of azafluorenone **341** (21.7 mg, 0.0650 mmol), and the mixture was stirred at 80 °C overnight. After allowing the reaction to cool to room temperature, water was added, and the mixture was extracted with EtOAc (3 x 20 mL). The combined organics were washed with water (3 x 10 mL), brine (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Aqueous NaOH-solution (2 M, 1.0 mL) and H_2O_2 (0.25 mL) were added to a solution of the crude product in THF (5.00 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 2 h. After the reaction completed, water (20 mL) was added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by FCC afforded the product **93** as a yellow solid (11.0 mg, 0.0431 mmol, 66%).

R_f: 0.29 (hexanes/EtOAc 1:1 + 1% NEt_3).

M.p.: 189 – 191°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.28 (d, *J* = 5.4 Hz, 1H, 3-H), 7.31 (s, 1H, 5-H), 7.19 (s, 1H, 8-H), 6.85 (dd, *J* = 5.4, 0.8 Hz, 1H, 2-H), 4.01 (s, 3H, 6-OCH_3), 3.95 (s, 3H, 7-OCH_3), 2.58 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 192.6 (C-9), 165.2 (C-4a), 155.0 (C-6), 152.1 (C-3), 151.3 (C-7), 146.7 (C-1), 138.1 (C-4b), 128.2 (C-8a), 126.5 (C-9a), 125.3 (C-2), 106.5 (C-8), 103.6 (C-5), 56.7 (6-OCH_3), 56.5 (7-OCH_3), 17.2 (CH_3).

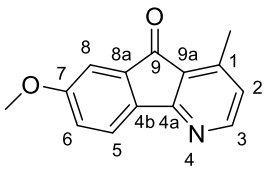
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2923, 1694, 1597, 1566, 1604, 1470, 1370, 1328, 1256, 1213, 1099, 1048, 1008, 866, 798, 764.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{13}NO_3^{\bullet+}$; 255.0895; found 255.0893.

HPLC purity (method 1b): >95% (210 nm), >95% (254 nm).

Literature known compound.[142]

7-Methoxyonychine (95)



$C_{14}H_{11}NO_2$

M = 225.2470 g/mol

This compound was prepared in accordance with **General procedure C** from

a) ester **133** (543 mg, 2.00 mmol) and PPA (5.50 g). Purification by FCC afforded the product **95** as yellow solid (38.7 mg, 0.172 mmol, 9%).
b) PPA (20.0 g) and crude carboxylic acid **134** (2.00 g) furnished from previous hydrolysis of ester **133** (3.64 g, 13.3 mmol) with KOH (3.00 g, 53.6 mmol) in accordance with General procedure **D**. Purification by FCC afforded the product **95** as yellow solid (452 mg, 2.00 mmol, 15% over two steps from ester **133**).

R_f: 0.40 (hexanes/EtOAc 2:1).

M.p.: 141 – 142 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.34 (d, *J* = 5.3 Hz, 1H, 3-H), 7.71 (d, *J* = 8.2 Hz, 1H, 5-H), 7.21 (d, *J* = 2.4 Hz, 1H, 8-H), 7.06 (dd, *J* = 8.2, 2.4 Hz, 1H, 6-H), 6.87 (dd, *J* = 5.4, 0.7 Hz, 1H, 2-H), 3.88 (s, 3H, OCH_3), 2.60 (d, *J* = 0.6 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 193.3 (C-9), 165.8 (C-4a), 162.4 (C-7), 152.9 (C-3), 147.5 (C-1), 137.1 (C-8a), 135.7 (C-4b), 126.2 (C-9a), 125.0 (C-2), 122.2 (C-5), 120.6 (C-6), 109.0 (C-8), 56.0 (OCH_3), 17.5 (CH_3).

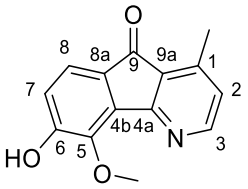
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1712, 1564, 1292, 1229, 1012, 832, 819, 797.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}NO_2^{\bullet+}$: 225.0790; found 225.0783.

HPLC purity (Method 3a): >95% (210 nm), >95% (254 nm).

Literature known compound.[136]

Ursuline (96)



$C_{14}H_{11}NO_3$

M = 241.2460 g/mol

This compound was prepared in accordance with **General procedure B** from azafluorenone **314** (48.7 mg, 0.160 mmol), $Pd_2(dba)_3$ (5.86 mg, 0.00640 mmol), Me_4*t*ButylXPhos (6.15 mg, 0.0128 mmol) and KOH (18.0 mg, 0.320 mmol). Purification by FCC afforded the product **96** as a brown-yellow solid (27.0 mg, 0.112 mmol, 70%).

R_f: 0.23 (hexanes/EtOAc 1:1).

M.p.: 150 °C.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 10.55 (s, 1H, OH), 8.48 (d, *J* = 5.3 Hz, 1H, 3-H), 7.31 (d, *J* = 8.0 Hz, 1H, 8-H), 7.20 – 7.11 (m, 1H, 2-H), 6.88 (d, *J* = 7.9 Hz, 1H, 7-H), 3.91 (s, 3H, OCH_3), 2.53 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 190.9 (C-9), 163.3 (C-4a), 158.3 (C-6), 152.6 (C-3), 146.1 (C-1), 143.6 (C-5), 134.5 (C-5a), 126.8 (C-8a), 126.2 (C-9a), 125.5 (C-2), 121.1 (C-8), 117.7 (C-7), 61.0 (OCH_3), 16.6 (CH_3).

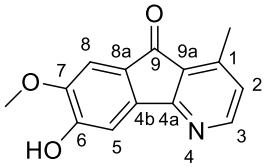
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3443, 2926, 1705, 1597, 1564, 1490, 1437, 1378, 1271, 1227, 1012, 800.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}NO_3^{\bullet+}$: 241.0739; found 241.0730.

HPLC purity (Method 1a): >95% (210 nm), >95% (254 nm).

Literature known compound.[254]

Oncodine (97)



$C_{14}H_{11}NO_3$

M = 241.2460 g/mol

This compound was prepared in accordance with **General procedure B** from

a) azafluorenone **292** (103 mg, 0.340 mmol), $Pd_2(dba)_3$ (12.5 mg, 0.0136 mmol), Me_4*t*ButylXPhos (13.1 mg, 0.0272 mmol) and KOH (76.3 mg, 1.36 mmol). Purification by FCC afforded the product **97** as an orange solid (59.3 mg, 0.246 mmol, 72%).
b) azafluorenone **294** (146 mg, 0.380 mmol), $Pd_2(dba)_3$ (27.8 mg, 0.0304 mmol), Me_4*t*ButylXPhos (29.2 mg, 0.0608 mmol) and KOH (128 mg, 2.28 mmol). Purification by FCC afforded the product azafluorenone **97** as a yellow-orange solid (58.0 mg, 0.240 mmol, 63%) and azafluorenone **92** as a yellow solid (23 mg, 0.0894 mmol, 23%).

R_f: 0.36 (hexanes/EtOAc 4:1 + 1% AcOH).

M.p.: 255 – 256 °C (decomposition).

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 10.51 (s, 1H, OH), 8.31 (d, J = 5.4 Hz, 1H, 3-H), 7.18 (s, 1H, 8-H), 7.13 (s, 1H, 5-H), 7.02 (d, J = 5.4 Hz, 1H, 2-H), 3.86 (s, 3H, OCH_3).

The ^{1}H CH_3-signal overlaps with the DMSO-signal but is clearly visible in ^{13}C and 2-D NMR spectra.

^{13}C NMR (101 MHz, $(CD_3)_2SO$): 192.0 (C-9), 164.7 (C-4a), 154.2 (C-6), 152.5 (C-3), 150.4 (C-7), 146.0 (C-1), 138.1 (C-4b), 126.5 (C-8a), 126.2 (C-9a), 125.7 (C-2), 108.1 (C-5), 107.8 (C-8), 56.5 (OCH_3), 16.9 (CH_3).

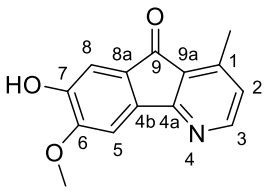
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3000, 1710, 1567, 1466, 1346, 1270, 1210, 1133, 1023, 800.

HRMS (ESI): *m/z* = $[M+H]^+$ calcd for $C_{14}H_{12}NO_3^+$: 242.0812; found 242.0814.

HPLC purity (Method 3b): >95% (210 nm), >95% (254 nm).

Literature known compound.[93, 254]

Isooncodine (98)



$C_{14}H_{11}NO_3$

M = 241.2460 g/mol

This compound was prepared in accordance with **General procedure B** from azafluorenone **288** (10.0 mg, 0.033 mmol), $Pd_2(dba)_3$ (1.21 mg, 0.00132 mmol), Me_4*t*ButylXPhos (1.27 mg, 0.00264 mmol) and KOH (7.41 mg, 0.132 mmol). Attempts at purification by FCC and preparative TLC afforded the crude product **98** as a brown solid (5 mg, 0,021 mmol, 63% crude yield).

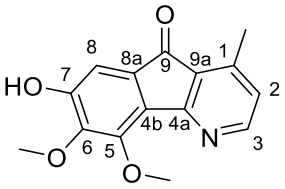
R_f: 0.36 (hexanes/EtOAc 4:1 + 1% AcOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.3 (d, *J* = 5.4 Hz, 1H), 7.3 (s, 1H,), 7.2 (s, 1H,), 6.9 (d, *J* = 5.4 Hz, 1H,), 4.0 (s, 3H,), 2.6 (s, 3H).

HRMS (ESI): *m/z* = $[M+H]^+$ calcd for $C_{14}H_{12}NO_3^+$: 242.0812; found 242.0816.

Literature known compound.[91]

Darienine (99)



$C_{15}H_{13}BrNO_4$

M = 271.2720 g/mol

This compound was prepared in accordance with **General procedure B** from azafluorenone **283** (70.2 mg, 0.210 mmol), $Pd_2(dba)_3$ (7.69 mg, 0.00840 mmol), Me_4*t*ButylXPhos (8.08 mg, 0.0168 mmol) and KOH (23.6 mg, 0.420 mmol). Purification by FCC afforded the product **99** as a yellow solid (18.0 mg, 0.0664 mmol, 32%).

R_f: 0.36 (hexanes/EtOAc 1:1).

M.p.: 180 – 181°C.

^{1}H NMR (500 MHz, CD_3CN): δ (ppm) = 8.35 (d, J = 5.3 Hz, 1H, 3-H), 7.32 (s, 1H, OH), 6.94 (s, 1H, 8-H), 6.94 – 6.92 (m, 1H, 2-H), 4.03 (s, 3H, 5-OCH_3), 3.96 (s, 3H, 6-OCH_3), 2.52 (s, 3H, CH_3).

^{13}C NMR (126 MHz, CD_3CN): δ (ppm) = 193.0 (C-9), 165.8 (C-4a), 153.7 (C-7), 153.5 (C-3), 150.5 (C-5), 147.6 (C-1), 147.2 (C-6), 132.6 (C-8a), 127.8 (C-4b), 126.6 (C-9a), 125.2 (C-2), 107.9 (C-8), 62.3 (5-OCH_3), 62.0 (6-OCH_3), 17.2 (CH_3).

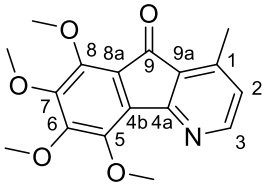
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3363, 2946, 1705, 1607, 1557, 1464, 1337, 1320, 1109, 1073, 947, 870, 802.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{13}{}^{79}BrNO_4{}^{\bullet+}$: 271.0845; found 271.0834.

HPLC purity (Method 1b): >95% (210 nm), >95% (254 nm).

Literature known compound.[75a]

5,6,7,8-Tetramethoxyonychine (100)



$C_{15}H_{17}NO_5$

M = 315.3250 g/mol

This compound was prepared in accordance with **General procedure A2** from pyridinemethanol **320** (99.0 mg, 0.310 mmol) and TBHP (5.5 M in decane, 0.451 mL, 2.48 mmol). Purification by FCC afforded the product **100** as a yellow solid (14.0 mg, 0.0444 mmol, 14%).

R_f: 0.38 (hexanes/EtOAc 2:1).

M.p.: 73 – 74 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.45 (d, J = 5.2 Hz, 1H, 3-H), 6.89 (dd, J = 5.2, 0.7 Hz, 1H, 2-H), 4.05 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 2.61 (d, J = 0.7 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 190.1 (C-9), 163.6 (C-4a), 153.9 ($\underline{C}OCH_3$), 152.8 (C-3), 149.8 ($\underline{C}OCH_3$), 148.8 ($\underline{C}OCH_3$), 146.9 (C-1), 145.9 ($\underline{C}OCH_3$), 129.8 (C-4b or C-8a), 126.5

(C-9a), 125.0 (C-2), 121.1 (C-4b or C-8a), 62.1 (OCH_3), 61.9 (OCH_3), 61.7 (OCH_3), 61.6 (OCH_3), 17.3 (CH_3).

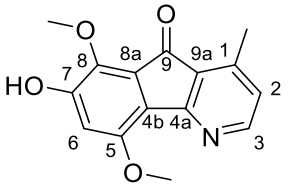
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2931, 2844, 1698, 1559, 1461, 1386, 1276, 1199, 1109, 1072, 1028, 977, 846.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{17}H_{17}NO_5^{\bullet+}$: 315.1107; found 315.1099.

HPLC purity (Method 1b): >95% (210 nm), >95% (254 nm).

Literature known compound.[94]

7-Hydroxy-5,8-dimethoxyonychine (101)



$C_{15}H_{13}NO_4$

M = 271.2720 g/mol

This compound was prepared in accordance with **General procedure B** from azafluorenone **326** (60.2 mg, 0.180 mmol), $Pd_2(dba)_3$ (6.59 mg, 0.00720 mmol), Me_4*t*ButylXPhos (6.92 mg, 0.0144 mmol) and KOH (30.3 mg, 0.540 mmol). Purification by FCC afforded the product **101** as an orange-red solid (29.0 mg, 0.107 mmol, 59%).

R_f: 0.26 (EtOAc).

M.p.: 206 – 208 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.42 (d, *J* = 5.3 Hz, 1H, 3-H), 6.81 (dd, *J* = 5.3, 0.7 Hz, 1H, 2-H), 6.75 (s, 1H, 6-H), 6.41 (s, 1H, OH), 4.09 (s, 3H, 8-OCH_3), 3.98 (s, 3H, 5-OCH_3), 2.59 (d, 3H, *J* = 0.7 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.2 (C-9), 165.5 (C-4a), 153.2 (C-7), 153.1 (C-3), 152.5 (C-5), 147.3 (C-1), 139.5 (C-8), 125.9 (C-9a), 125.3 (C-8a), 124.0 (C-2), 120.4 (C-4b), 105.5 (C-6), 62.7 (8-OCH_3), 56.7 (5-OCH_3), 17.5 (CH_3).

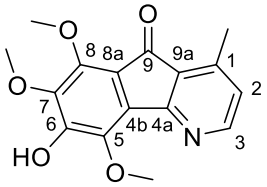
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3175, 2924, 1702, 1606, 1556, 1491, 1440, 1310, 1268, 1036, 974, 810, 791.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{13}NO_4^{\bullet+}$: 271.0845; found 271.0837.

HPLC purity (Method 1c): >95% (210 nm), >95% (254 nm).

Literature-known compound.[95]

Muniranine (103)



$C_{16}H_{15}NO_5$

M = 301.2980 g/mol

This compound was prepared in accordance with **General procedure B** from azafluorenone **338** (40.1 mg, 0.110 mmol), $Pd_2(dba)_3$ (4.03 mg, 0.00440 mmol), Me_4*t*ButylXPhos (4.23 mg, 0.0880 mmol) and KOH (24.7 mg, 0.440 mmol). Purification by preparative TLC afforded the product **103** as a yellow film (21.0 mg, 0.0697 mmol, 63%).

R_f: 0.60 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.44 (d, *J* = 5.3 Hz, 1H, 3-H), 6.90 (d, *J* = 5.3 Hz, 1H, 2-H), 4.10 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 2.61 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 189.9 (C-9), 163.2 (C-4a), 152.6 (C-3), 149.8 ($COCH_3$ or COH), 149.7 ($\underline{C}OCH_3$ or C-6), 146.9 (C-1), 142.1 ($\underline{C}OCH_3$ or C-6), 140.0 ($COCH_3$ or COH), 129.6 (C-4b or C-8a), 126.9 (C-9a), 125.2 (C-2), 118.1 (C-4b or C-8a), 62.3 (OCH_3), 62.2 (OCH_3), 61.6 (OCH_3), 17.3 (CH_3).

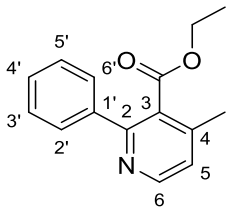
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2930, 1697, 1559, 1458, 1397, 1287, 1131, 1067, 1025, 981, 948, 809.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{16}H_{15}NO_5^{\bullet+}$: 301.0950; found 301.0944.

HPLC purity (Method 2a): >95% (210 nm), >95% (254 nm).

Literature known compound.[232]

Ethyl 4-methyl-2-phenylnicotinate (130)



$C_{15}H_{15}NO_2$

M = 241.2900 g/mol

This compound was prepared in accordance with **General procedure E** from commercially available β-ketoester **129** (6.00 g, 28.1 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 2.81 mL, 6.18 mmol), crotonaldehyde (3.72 mL, 45.0 mmol) and hydroxylammonium chloride (6.44 g, 92.7 mmol). Purification by FCC afforded the product **130** as a yellow oil (2.69 g, 11.1 mmol, 40%).

R_f: 0.32 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.55 (d, J = 5.1 Hz, 1H, 6-H), 7.59–7.55 (m, 2H, 2‘-H), 7.44–7.40 (m, 3H, 3‘-H and 4‘-H), 7.16 (dd, J = 5.0, 0.7 Hz, 1H, 5-H), 4.14 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 2.41 (d, J = 0.7 Hz, 3H, CH_3), 1.05 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$).

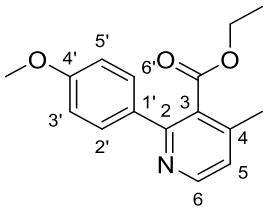
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 169.0 (COO), 156.7 (C-2), 150.0 (C-6), 145.9 (C-4), 140.6 (C-1’), 129.7 (C-3), 128.9 (C-4’), 128.7 (C-3’), 128.6 (C-2’), 124.0 (C-5), 61.8 ($O\underline{C}H_2CH_3$), 19.5 (CH3), 13.9 ($OCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2978, 1720, 1572, 1441, 1270, 1238, 1131, 1105, 1063, 763, 678.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{15}NO_2^{\bullet+}$: 241.1103; found 241.1096.

Literature known compound.[129]

Ethyl 2-(4-methoxyphenyl)-4-methylnicotinate (133)



$C_{16}H_{17}NO_3$

M = 271.3160 g/mol

This compound was prepared in accordance with **General procedure E** from commercially available β-ketoester **132** (5.00 g, 22.5 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 2.25 mL, 4.95 mmol), crotonaldehyde (2.42 mL, 29.3 mmol) and hydroxylammonium chloride (5.16 g, 74.3 mmol). Purification by FCC afforded the product **133** as an amber colored oil (610 mg, 2.21 mmol, 10%).

This compound was also prepared in accordance with **General procedure 2** from commercially available β-ketoester **132** (25.0 g, 113 mmol), NaH (60% dispersed in mineral oil, 540 mg, 13.5 mmol), crotonaldehyde (13.0 mL, 158 mmol) and hydroxylammonium chloride (32.1 g, 461 mmol). Purification by FCC afforded the product **133** as an amber colored oil (6.97 g, 25.7 mmol, 23%).

R_f: 0.28 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.54 (d, J = 5.1 Hz, 1H, 6-H), 7.57 – 7.51 (m, 2H, 2'-H), 7.09 (dd, J = 5.2, 0.8 Hz, 1H, 5-H), 7.00 – 6.90 (m, 2H, 3'-H), 4.18 (q, J = 7.1 Hz, 2H, $COOC\underline{H}_2CH_3$), 3.84 (s, 3H, OCH_3), 2.40 (d, J = 0.7 Hz, 3H, CH_3), 1.09 (t, J = 7.1 Hz, 3H, $COOCH_2C\underline{H}_3$).

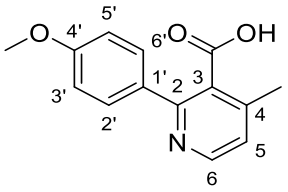
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 169.1 (COO), 160.2 (C-4'), 156.3 (C-2), 149.7 (C-6), 145.5 (C-4), 132.7 (C-1'), 129.8 (C-2'), 129.1 (C-3), 123.3 (C-5), 113.9 (C-3'), 61.6 ($COO\underline{C}H_2CH_3$), 55.5 (OCH_3), 19.5 (CH_3), 14.0 ($COOCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2979, 1720, 1609, 1513, 1444, 1419, 1248, 1175, 1130, 1102, 1064, 1029, 833, 791.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{16}H_{17}NO_3^{\bullet+}$: 271.1208; found 271.1201.

Literature known compound.[136]

2-(4-Methoxyphenyl)-4-methylnicotinic acid (134)



$C_{14}H_{13}NO_3$

M = 243.2620 g/mol

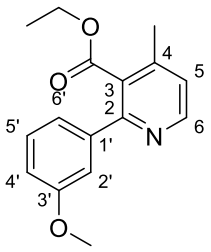
This compound was prepared in accordance with **General procedure D** from ester **133** (6.40 g, 23.6 mmol) and KOH (5.30 g, 94.4 mmol). The crude product **134** was afforded as a white solid (3.64 g, 15.0 mmol, 63%) and used without further purification.

R_f: 0.35 (DCM/MeOH 4:1).

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 8.43 (d, J = 5.0 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 5.0 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H), 2.29 (s, 3H).

HRMS (EI): *m/z* = $[M+H]^{\bullet+}$ calcd for $C_{14}H_{14}NO_3^{\bullet+}$: 244.0968; found 244.0969.

Ethyl 2-(3-methoxyphenyl)-4-methylnicotinate (159)



$C_{16}H_{17}NO_3$

M = 271.3160 g/mol

This compound was prepared in accordance with **General procedure E** from β-ketoester **286** (15.6 g, 70.0 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 7.00 mL, 15.4 mmol), crotonaldehyde (8.70 mL, 105 mmol) and hydroxylammonium chloride (16.1 g, 231 mmol). Purification by FCC afforded the product **159** as an amber-colored oil (5.17 g, 19.0 mmol, 27%).

R_f: 0.18 (hexanes/EtOAc 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) = 8.56 (d, *J* = 5.0 Hz, 1H, 6-H), 7.34 – 7.28 (m, 1H, 5‘-H), 7.16 – 7.12 (m, 3H, 5-H and 2‘-H and 6‘-H), 6.95 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H, 4‘-H), 4.15 (q, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 3.84 (s, 3H, OCH_3), 2.42 (d, *J* = 0.7 Hz, 3H, CH_3), 1.05 (t, *J* = 7.2 Hz, 3H, $CH_2C\underline{H}_3$).

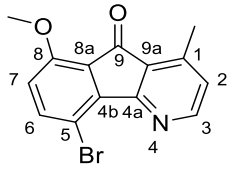
^{13}C NMR (101 MHz, $CDCl_3$): *δ* (ppm) = 168.8 (COO), 159.7 (C-3’), 156.7 (C-2), 149.7 (C-6), 145.7 8 (C-4), 141.5 (C-1’), 129.5 (C-3), 129.5 (C-5’), 123.9 (C-5), 120.9 (C-2’ or C-6’), 115.2 (C-4’), 113.4 (C-2’ or C-6’), 61.6 ($\underline{C}H_2CH_3$), 55.5 (OCH_3), 19.5 (CH_3), 13.8 ($CH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2980, 1720, 1574, 1429, 1271, 1234, 1128, 1064, 1039, 779, 697.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{16}H_{17}NO_3^{\bullet+}$: 271.1208; found: 271.1206.

Literature known compound.[139]

5-Bromo-8-methoxyonychine (163)



$C_{14}H_{10}BrNO_2$

M = 304.1430 g/mol

This compound was prepared in accordance with **General procedure F** from azafluorenone **164** (20.3 mg, 0.0900 mmol) and NBS (17.6 mg, 0.0990 mmol). Purification by FCC afforded the product **163** as yellow solid (14.3 mg, 0.0470 mmol, 52%).

R_f: 0.37 (hexanes /EtOAc 4:1 + 1% AcOH).

M.p.: 200 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.55 (d, J = 5.3 Hz, 1H, 3-H), 7.63 (d, J = 8.9 Hz, 1H, 6-H), 7.01 (d, J = 5.3 Hz, 1H, 2-H), 6.85 (d, J = 8.9 Hz, 1H, 7-H), 3.99 (s, 3H, OCH_3), 2.63 (s, 3H, CH_3)

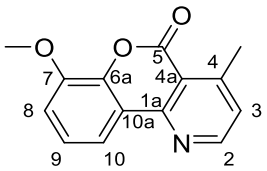
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 190.3 (C-9), 163.6 (C-4a), 157.4 (C-8), 152.2 (C-3), 147.5 (C-1), 141.9 (C-6), 141.7 (C-4b), 126.3 (C-9a), 126.3 (C-2), 122.9 (C-8a), 116.4 (C-7), 107.4 (C-5), 56.4 (OCH_3), 17.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1701, 1584, 1561, 1373, 1269, 1162, 1111, 941, 823, 722.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{14}H_{10}{}^{79}BrNO_2{}^{\bullet+}$: 302.9895; found 302.9890.

Literature known compound.[199]

7-Methoxy-4-methyl-5*H*-chromeno[4,3-*b*]pyridin-5-one (176)



$C_{14}H_{11}NO_3$

M = 241.2460 g/mol

This compound was prepared in accordance with **General procedure E** from β-ketoester **300** (353 mg, 1.00 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 0.100 mL, 0.220 mmol), crotonaldehyde (0.124 mL, 1.50 mmol) and hydroxylammonium chloride (229 mg, 3.30 mmol). Purification by FCC afforded the product **176** as a white solid (50.1 mg, 0.207 mmol, 21%).

R_f: 0.38 (hexanes/EtOAc 4:1).

M.p.: 159 – 160 °C.

^{1}H NMR (500 MHz, CD_3Cl): δ (ppm) = 8.80 (d, *J* = 4.9 Hz, 1H, 2-H), 8.17 (dd, *J* = 8.1, 1.4 Hz, 1H, 10-H), 7.32 – 7.28 (m, 2H, 3-H and 9-H), 7.12 (dd, *J* = 8.1, 1.4 Hz, 1H, 8-H), 3.99 (s, OCH_3), 2.89 (d, *J* = 0.8 Hz, CH_3).

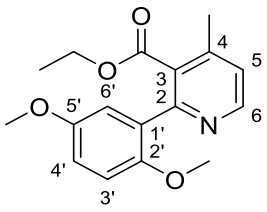
^{13}C NMR (101 MHz, CD_3Cl): δ (ppm) = 159.9 (C-5), 154.1 (C-2), 153.9 (C-4), 153.2 (C-1a), 147.4 (C-7), 142.4 (C6a), 126.9 (C-3), 124.4 (C-9), 120.3 (C-4a), 116.7 (C-10a), 116.7 (C-10), 113.9 (C-8), 56.5 (OCH_3), 23.2 (CH_3).

IR (ATR): 2358, 1721, 1574, 1494, 1440, 1393, 1275, 1240, 1210, 1181, 1054, 926, 764, 732.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}NO_3^{\bullet+}$: 241.0739; found 241.0733.

Literature known compound.[144]

Ethyl 2-(2,5-dimethoxyphenyl)-4-methylnicotinate (177)



$C_{17}H_{19}NO_4$

M = 301.3420 g/mol

This compound was prepared in accordance with **General procedure E** from β-ketoester **328** (19.0 g, 67.2 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 9.10 mL, 20.0 mmol), crotonaldehyde (9.05 mL, 109 mmol) and hydroxylammonium chloride (20.9 g, 300 mmol). Purification by FCC afforded the product **177** as an amber colored oil (9.15 g, 30.4 mmol, 45%)

R_f: 0.26 (hexanes/EtOAc 4:1 + 1% NEt_3).

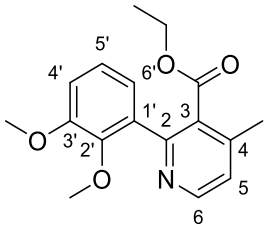
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.58 (d, J = 5.0 Hz, 1H, 6-H), 7.15 – 7.13 (m, 1H, 5-H), 6.97 (d, J = 3.0 Hz, 1H, 6‘-H), 6.90 (dd, J = 8.9, 3.1 Hz, 1H, 4‘-H), 6.83 (d, J = 8.9 Hz, 1H, 3‘-H), 4.07 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 3.78 (s, 3H, 5’-OCH_3), 3.69 (s, 3H, 2‘-OCH_3), 2.47 (d, J = 0.7 Hz, 3H, CH_3), 0.99 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 167.7 (COO), 155.3 (C-2), 153.7 (C-5’), 150.8 (C-2’), 149.9 (C-6), 146.1 (C-4), 130.4 (C-1’), 129.9 (C-3), 124.3 (C-5), 115.9 (C-6’), 115.5 (C-4’), 111.9 (C-3’), 61.0 ($O\underline{C}H_2CH_3$), 56.1 (2’-OCH_3), 56.0 (5’-OCH_3), 20.2 (CH_3), 13.8 ($OCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2935, 2833, 1721, 1575, 1498, 1427, 1270, 1213, 1127, 1042, 807, 716.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{17}H_{19}NO_4^{\bullet+}$: 301.1314 found 301.1307.

Ethyl 2-(2,3-dimethoxyphenyl)-4-methylnicotinate (178)



$C_{17}H_{19}NO_4$

M = 301.3420 g/mol

This compound was prepared in accordance with **General procedure E** from β-ketoester **277** (12.0 g, 40.0 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 4.00 mL, 8.80 mmol), crotonaldehyde (4.97 mL, 60.0 mmol) and hydroxylammonium chloride (9.17 g, 132 mmol). Purification by FCC afforded the product **178** as a yellow oil (6.92 g, 23.0 mmol, 57%).

R_f: 0.43 (hexanes/EtOAc 1:1).

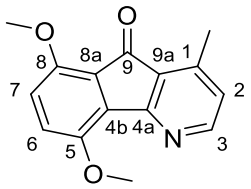
^{1}H NMR (400 MHz, MeOD): δ (ppm) = 8.50 (d, J = 5.2 Hz, 1H, 6-H), 7.38 (dd, J = 5.1, 0.8 Hz, 1H, 5-H), 7.14 – 7.12 (m, 2H, 5‘-H and 6‘-H), 6.86 (dd, J = 5.6, 3.5 Hz, 1H, 4‘-H), 4.08 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 3.91 (s, 3H, 3‘-OCH_3), 3.59 (s, 3H, 2‘-OCH_3), 2.48 (d, J = 0.7 Hz, 3H, CH_3), 0.97 (t, J = 7.1 Hz, 3H, OCH_2CH_3).

^{13}C NMR (101 MHz, MeOD): δ (ppm) = 168.7 (COO), 156.0 (C-2), 154.1 (C-3’), 150.0 (C-6), 148.2 (C-4), 148.1 (C-2’), 135.3 (C-1’), 131.8 (C-3), 125.8 (C-5), 124.9 (C-5’), 123.1 (C-4’), 114.5 (C-6’), 62.3 ($O\underline{C}H_2CH_3$), 61.1 (2’-OCH_3), 56.5 (3’-OCH_3), 19.8 (CH_3), 13.9 ($OCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2978, 2935, 1720, 1575, 1475, 1425, 1318, 1261, 1232, 1121, 1058, 1004, 783.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{17}H_{19}NO_4^{\bullet+}$: 301.3420; found 301.1307.

5,8-Dimethoxyonychine (180)



$C_{15}H_{13}NO_3$

M = 255.2730 g/mol

This compound was prepared in accordance with **General procedure A2** from pyridinemethanol **329** (786 mg, 3.03 mmol) and TBHP (5.5 M in decane, 2.20 mL, 12.1 mmol). Purification by FCC afforded the product **180** as a yellow solid (160 mg, 0.627 mmol, 21%).

R_f: 0.23 (EtOAc).

M.p.: 154 – 155 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.49 (d, *J* = 5.3 Hz, 1H, 3-H), 7.14 (d, *J* = 9.1 Hz, 1H, 6-H or 7-H), 6.94 (d, *J* = 9.1 Hz, 1H, 6-H or 7-H), 6.91 (dd, *J* = 5.3, 0.8 Hz, 1H, 2-H), 4.02 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 2.61 (d, *J* = 0.7 Hz, 3H, CH_3).

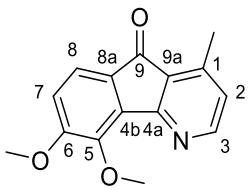
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.54 (C-9), 164.40 (C-4a), 152.75 (C-3), 152.43 (C-5), 149.64 (C-8), 147.27 (C-1), 129.87 (C-4b or C-8a), 125.81 (C-9a), 125.16 (C-2), 121.98 (C-4b or C-8a), 121.30 (C-7), 116.49 (C-6), 56.87 (OCH_3), 56.39 (OCH_3), 17.41 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3229, 2939, 1699, 1564, 1500, 1451, 1257, 1176, 1045, 957, 810.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{13}NO_3^{\bullet+}$: 255.0895; found 255.0896.

Literature known compound.[87]

5,6-Dimethoxyonychine (181)



$C_{15}H_{13}NO_3$

M = 255.2730 g/mol

This compound was prepared in accordance with **General procedure A2** from pyridinemethanol **278** (130 mg, 0.500 mmol) and $TBHP_{dec}$ (5.5 M, 0.485 mL, 4.00 mmol). Purification by FCC afforded the product **181** as a yellow solid (31.0 mg, 0.121 mmol, 24%).

R_f: 0.43 (hexanes/EtOAc 1:1).

M.p.: 130 – 131°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.50 (d, J = 5.3 Hz, 1H, 3-H), 7.48 (d, J = 8.0 Hz, 1H, 8-H), 6.94 (dd, J = 5.2, 0.8 Hz, 1H, 2-H), 6.86 (d, J = 8.1 Hz, 1H, 7-H), 4.05 (s, 3H, 5-OCH_3), 3.95 (s, 3H, 6-OCH_3), 2.62 (s, 3H, CH_3).

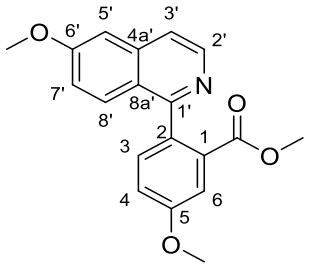
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 192.0 (C-9), 164.3 (C-4a), 159.8 (C-6), 153.0 (C-3), 147.1 (C-1), 145.5 (C-5), 134.7 (C-4b), 129.0 (C-8a), 127.2 (C-9a), 125.4 (C-2), 121.0 (C-8), 112.9 (C-7), 61.7 (5-OCH_3), 56.5 (6-OCH_3), 17.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2921, 1760, 1702, 1595, 1563, 1357, 1243, 1081, 919, 878, 828, 756.

HRMS (EI): m/z = $[M-H]^{\bullet-}$ calcd for $C_{15}H_{12}NO_3^{\bullet-}$: 254.0817; found 254.0811.

Literature known compound.[87]

Methyl 5-methoxy-2-(6-methoxyisoquinolin-1-yl)benzoate (182)



$C_{19}H_{17}NO_4$

M = 323.3480 g/mol

This compound was prepared in accordance with **General procedure G** from isoquinoline **373** (2.00 g, 7.00 mmol), boronic acid pinacol ester **372** (2.45 g, 8.40 mmol), $Pd(PPh_3)_4$ (404 mg, 0.350 mmol) and K_2CO_3 (4.21 g, 42.1 mmol). Purification by FCC afforded the product **182** as a yellow oil (932 mg, 2.88 mmol, 41%).

R_f: 0.64 (hexanes/EtOAc 4:1 + 1% NEt_3).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.47 (d, *J* = 5.7 Hz, 1H, 3'-H), 7.59 (d, *J* = 2.7 Hz, 1H, 6-H), 7.57 – 7.51 (m, 2H, 4'-H and 8'-H), 7.41 (d, *J* = 8.4 Hz, 1H, 3-H), 7.17 (dd, *J* = 8.4, 2.7 Hz, 4-H), 7.13 – 7.05 (m, 2H, 5'-H and 7'-H), 3.95 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.43 (s, $COOCH_3$).

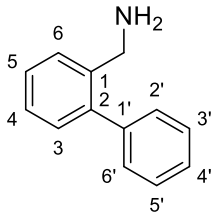
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 167.3 (COO), 160.6 (C-6'), 160.3 (C-1'), 159.6 (C-5), 142.7 (C-3'), 138.2 (C-4a'), 133.4 (C-2), 132.2 (C-3), 132.1 (C-1), 128.8 (C-4' or C-8'), 123.5 (C-8a'), 120.0 (C-5'), 119.3 (C-4' or C-8'), 118.1 (C-4), 115.1 (C-6), 104.6 (C-7'), 55.8 (5-OCH_3), 55.6 (6'-OCH_3), 52.1 (COO<u>C</u>H_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954, 1712, 1620, 1466, 1435, 1357, 1211, 1278, 1253, 1221, 1183, 1026, 985, 857, 837, 792, 782, 680.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{19}H_{17}NO_4^{\bullet+}$: 323.1158; found 323.1150.

Literature known compound. The synthesis was performed as described by Melzer et al.[235]

2-Phenylbenzylamine (184)



$C_{13}H_{13}N$

M = 183.2540 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188** (1.32 g, 7.36 mmol), LAH (838 mg, 22.1 mmol) and $AlCl_3$ (2.94 g, 22.1 mmol). Purification by FCC afforded the product **184** as a yellow oil (1.19 g, 6.49 mmol, 88%).

R_f: 0.35 (hexanes/EtOAc 1:1 + NEt_3 1%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 7.58 (dd, *J* = 7.7, 1.4 Hz, 1H, 6-H), 7.47 – 7.40 (m, 2H, 2'-H and 6'-H or 3'-H and 6'-H), 7.39 – 7.32 (m, 4H, 2'-H and 6'-H and H_{arom} or 3'-H and 6'-H and H_{arom}), 7.28 (td, *J* = 7.4, 1.5 Hz, 1H, 4-H), 7.17 (dd, *J* = 7.5, 1.5 Hz, 1H, 3-H), 3.62 (s, 2H, C<u>H_2</u>NH_2).

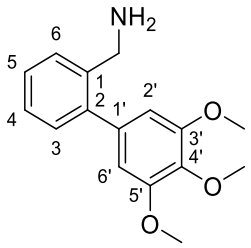
^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 141.1 (C-2), 140.9 (C-1 or C-1'), 140.4 (C-1 or C-1'), 129.4 (C-3), 129.0 (C-2' and C-6' or C-3' and C-5'), 128.2 (C-2' and C-6' or C-3' and C-5'), 128.2 (C-6), 127.4 (C-5), 127.0 (C-4'), 126.2 (C-4), 43.2 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3353, 3286, 3057, 3020, 2929, 2869, 1593, 1476, 1449, 1435, 1343, 1333, 1069, 1008, 914, 891, 774, 759, 749, 700.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{13}H_{13}N^{\bullet+}$: 183.1048; found 183.1049.

Literature known compound.[166]

2-(3,4,5-Trimethoxyphenyl)benzylamine (184a)



$C_{16}H_{19}NO_3$

M = 273.3320 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188a** (474 mg, 1.76 mmol), LAH (134 mg, 3.52 mmol) and $AlCl_3$ (469 mg, 3.52 mmol). Purification by FCC afforded the product **184a** as a yellow oil (327 mg, 1.20 mmol, 68%).

R_f: 0.19 (DCM/MeOH 1% + NEt_3 1%).

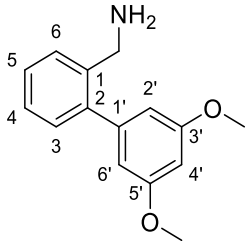
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.48 (ddd, *J* = 7.4, 1.6, 0.6 Hz, 1H, 6-H), 7.34 (td, *J* = 7.4, 1.8 Hz, 1H, 5-H), 7.30 (td, *J* = 7.3, 1.6 Hz, 1H, 4-H), 7.27 – 7.23 (m, 1H, 3-H), 6.59 (s, 2H, 2'-H and 6'-H), 3.83 (s, 6H, 3'-OCH_3 and 5'-OCH_3), 3.82 (s, 3H, 4'-OCH_3), 3.82 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 153.6 (C-3' and C-5'), 142.1 (C-2), 140.2 (C-1'), 137.7 (C-4'), 137.2 (C-1), 130.4 (C-3), 128.8 (C-6), 128.2 (C-5), 127.4 (C-4), 107.0 (C-2' and C-6'), 61.0 (4'-OCH_3), 56.6 (3'-OCH_3 and 5'-OCH_3), 44.3 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2962, 2936, 2827, 1581, 1506, 1451, 1407, 1342, 1183, 1155, 1118, 1002, 831, 766, 670.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{16}H_{19}NO_3^{\bullet+}$: 273.1365; found 273.1360.

2-(3,5-Dimethoxyphenyl)benzylamine (184b)



$C_{15}H_{17}NO_2$

M = 243.3060 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188b** (502 mg, 2.10 mmol), LAH (159 mg, 4.20 mmol) and $AlCl_3$ (560 mg, 4.20 mmol). Purification by FCC afforded the product **184b** as a yellow oil (244 mg, 1.00 mmol, 48%).

R_f: 0.17 (DCM/MeOH 1% + NEt_3 1%).

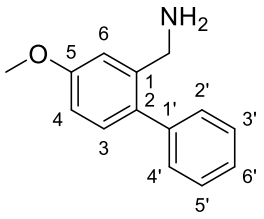
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.45 (ddd, J = 7.4, 1.5, 0.6 Hz, 1H, 6-H), 7.37 – 7.31 (m, 1H, 5-H), 7.27 (td, J = 7.4, 1.5 Hz, 1H, 4-H), 7.24 – 7.19 (m, 1H, 3-H), 6.50 (d, J = 2.3 Hz, 2H, 2'-H and 6'-H), 6.46 (t, J = 2.3 Hz, 1H, 4'-H), 3.80 (s, 6H, OCH_3), 3.78 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 161.2 (C-3' and C-5'), 143.9 (C-1'), 141.8 (C-2), 141.5 (C-1), 130.2 (C-3), 128.6 (C-6), 128.2 (C-5), 127.0 (C-4), 107.8 (C-2' and C-6'), 99.5 (C-4'), 55.9 (OCH_3), 44.7 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2936, 2906, 2837, 2645, 1586, 1454, 1417, 1322, 1199, 1148, 1061, 1026, 927, 830, 768, 700.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{17}NO_2^{\bullet+}$: 243.1259; found 243.1267.

5-Methoxy-2-phenylbenzylamine (184c1)



$C_{14}H_{15}NO$

M = 213.2800 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188c1** (879 mg, 4.20 mmol), LAH (638 mg, 16.8 mmol) and $AlCl_3$ (2.24 g, 16.8 mmol). Purification by FCC afforded the product **184c1** as a yellow oil (603 mg, 2.83 mmol, 67%).

R_f: 0.14 (DCM/MeOH 1% + NEt_3 1%).

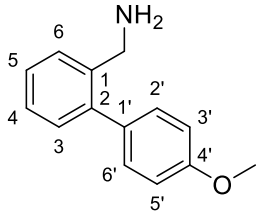
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.44 – 7.37 (m, 2H, 3'-H and 5'-H), 7.33 (tt, *J* = 7.9, 1.4 Hz, 3H, 2'-H and 6'-H and 4'-H), 7.15 (d, *J* = 8.3 Hz, 1H, 3-H), 7.04 (d, *J* = 2.7 Hz, 1H, 6-H), 6.83 (dd, *J* = 8.3, 2.7 Hz, 1H, 4-H), 3.84 (s, 3H, OCH_3), 3.74 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 159.6 (C-5), 142.8 (C-1), 141.5 (C-1'), 134.1 (C-2), 131.5 (C-3), 129.7 (C-2' and C-4'), 128.5 (C-3' and C-5'), 127.1 (C-6'), 113.8 (C-6), 112.2 (C-4), 55.7 (OCH_3), 44.6 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3368, 3026, 2934, 2834, 1606, 1567, 1506, 1480, 1464, 1442, 1419, 1273, 1228, 1162, 1047, 1006, 851, 815, 766, 700.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{15}NO^{\bullet+}$: 213.1154; found 213.1149.

2-(4-Methoxyphenyl)benzylamine (184c2)



$C_{14}H_{15}NO$

M = 213.2800 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188c2** (349 mg, 1.67 mmol), LAH (190 mg, 5.00 mmol) and $AlCl_3$ (312 mg, 2.34 mmol). Purification by FCC afforded the product **184c2** as a yellow solid (192 mg, 0.774 mmol, 46%).

R_f: 0.15 (DCM/MeOH 1% + NEt_3 1%).

M.p.: 40 – 44 °C.

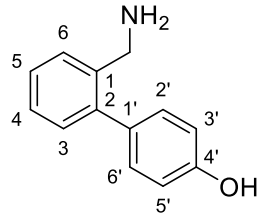
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.49 – 7.44 (m, 1H, 6-H), 7.32 (td, *J* = 7.4, 1.7 Hz, 1H, 5-H), 7.30 – 7.25 (m, 3H, 4-H and 2'-H and 6'-H), 7.23 – 7.19 (m, 1H, 3-H), 6.98 – 6.93 (m, 2H, 3'-H and 5'-H), 3.84 (s, 3H, OCH_3), 3.77 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 159.25 (C-4'), 141.36 (C-1), 141.25 (C-2), 133.93 (C-1'), 130.58 (C-2') and (C-6'), 130.54 (C-3), 128.48 (C-6), 127.72 (C-5), 126.99 (C-4), 113.97 (C-3' and C-5'), 55.65 (OCH_3), 44.45 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3359, 3273, 2934, 2835, 1954, 1579, 1496, 1478, 1446, 1432. 1251, 1230. 1182, 1159, 1120, 1050, 1021, 1003, 935, 906, 853, 806, 750, 742.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{15}NO^{\bullet+}$: 213.1154; found 213.1150.

2-(4-Hydroxyphenyl)benzylamine (184e)



$C_{13}H_{13}NO$

M = 199.2530 g/ mol

This compound was prepared in accordance with **General procedure H** from nitrile **188e** (390 mg, 2.00 mmol), LAH (342 mg, 9.00 mmol) and $AlCl_3$ (667 mg, 5.00 mmol). Purification by FCC afforded the product **184e** as a yellow white powder (222 mg, 1.11 mmol, 56%).

R_f: 0.49 (DCM/MeOH 1% + NEt_3 2%).

M.p.: 180 – 182 °C.

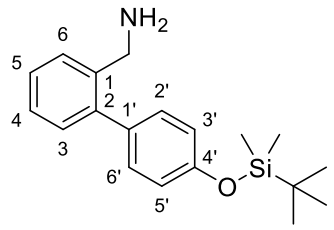
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 7.56 (dd, *J* = 7.7, 1.5 Hz, 1H, 6-H), 7.32 (td, *J* = 7.5, 1.6 Hz, 1H, 4-H), 7.27 (td, *J* = 7.4, 1.6 Hz, 1H, 5-H), 7.19 – 7.14 (m, 3H, 3-H and 2'-H and 6'-H), 6.88 – 6.79 (m, 2H, 3'-H and 5'-H), 3.71 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 156.6 (C-5), 140.8 (C-2), 138.7 (C-1), 131.1 (C-1'), 130.1 (C-2' and C-6'), 129.6 (C-3), 128.1 (C-6), 126.9 (C-4), 126.7 (C-5), 115.0 (C-3' and C-5'), 42.3 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3325, 2377, 2978, 2945, 2601, 2496, 1607, 1584, 1515, 1473, 1445, 1397, 1259, 1245, 1169, 1101, 1035, 941, 836, 804, 758.

HRMS (EI): *m/z* = $[M-H]^{\bullet-}$ calcd for $C_{13}H_{12}NO^{\bullet-}$: 198.0924; found 198.0911.

2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)benzylamine (184f)



$C_{19}H_{27}NOSi$

M = 313.5160 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188f** (501 mg, 1.62 mmol), LAH (215 mg, 5.67 mmol), $AlCl_3$ (648 mg, 4.86 mmol). Purification by FCC afforded the product **184f** as a white-yellow solid (380 mg, 1.21 mmol, 75%).

R_f: 0.15 (DCM/MeOH 1% + NEt_3 1%).

M.p.: 56 °C.

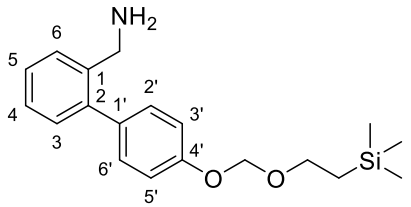
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.48 – 7.43 (m, 1H, 6-H), 7.32 (td, J = 7.4, 1.6 Hz, 1H, 5-H), 7.27 (td, J = 7.4, 1.6 Hz, 1H, 4-H), 7.24 – 7.19 (m, 3H, 3-H and 2'-H and 6'-H), 6.94 – 6.86 (m, 2H, 3'-H and 5'-H), 3.77 (s, 2H, $C\underline{H}_2NH_2$), 1.02 (9H, s, $C(C\underline{H}_3)_3$), 0.25 (6H, s, $Si(C\underline{H}_3)_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 155.3 (C-4'), 141.5 (C-1 or C-2), 141.4 (C-1 or C-2), 134.6 (C-1'), 130.6 (C-2' and C-6'), 130.5 (C-3), 128.4 (C-6), 127.7 (C-5), 126.9 (C-4), 120.1 (C-3' and C-5'), 44.5 (CH_2NH_2), 25.9 ($C(\underline{C}H_3)_3$), 18.5 ($\underline{C}(CH_3)_3$, -4.3 ($Si(\underline{C}H_3)_2$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954, 2928, 2857, 1606, 1512, 1478, 1248, 1168, 1097, 1005, 911, 835, 775, 764, 683.

HRMS (ESI): m/z = $[M+H]^+$ calcd for $C_{19}H_{28}NOSi^+$: 314.1935; found 314.1938.

2-(4-((2-(Trimethylsilyl)ethoxy)methoxy)phenyl)benzylamine (184g)



$C_{19}H_{27}NO_2Si$

M = 329.5150 g/mol

This compound was prepared in accordance with **General procedure H** nitrile **188g** (195 mg, 0.600 mmol), LAH (68.3 mg, 1.80 mmol) and $AlCl_3$ (240 mg, 1.80 mmol). Purification by FCC afforded the product **184g** as a yellow oil (136 mg, 0.413 mmol, 69%).

R_f: 0.14 (DCM/MeOH 1% + NEt_3 1%).

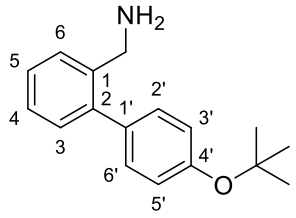
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.48 – 7.41 (m, 1H, H_{arom}), 7.35 – 7.19 (m, 5H, H_{arom}), 7.10 – 7.04 (m, 2H, 3'-H and 5'-H), 5.25 (d, J = 2.4 Hz, 2H, OCH_2O), 4.35 – 4.27 (m, 2H, $C\underline{H}_2NH_2$), 3.83 – 3.75 (m, 2H, $OC\underline{H}_2CH_2$), 1.03 – 0.93 (m, 2H, $OCH_2C\underline{H}_2$), 0.02 (d, J = 1.3 Hz, 9H, $Si(C\underline{H}_3)_3$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 157.1 (C-4'), 141.7 (C_{arom}), 139.0 (C_{arom}), 131.0 (C-2' and C-6'), 130.7 (C_{arom}), 130.7 (C_{arom}), 129.8 (C_{arom}), 127.7 (C_{arom}), 127.0 (C_{arom}), 116.3 (C-3' and C-5'), 93.6 (OCH_2O), 66.8 ($O\underline{C}H_2CH_2$), 53.8 (CH_2NH_2), 18.6 ($OCH_2\underline{C}H_2$), -1.2 ($Si(\underline{C}H_3)_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3346, 3013, 2938, 2897, 1605, 1504, 1486, 1434, 1221, 1167, 1087, 1019, 980, 945, 934, 867, 825, 743, 700.

HRMS (EI): *m/z* = $[M+H]^{\bullet+}$ calcd for $C_{19}H_{28}NO_2Si^{\bullet+}$: 330.1884; found 330.1886.

2-(4-(*tert*-Butoxy)phenyl)benzylamine (184h)



$C_{17}H_{21}NO$

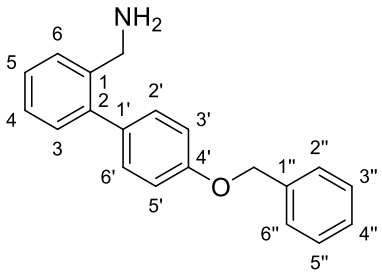
M = 255.3610 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188h** (426 mg, 1.86 mmol), LAH (212 mg, 5.58 mmol) and $AlCl_3$ (744 mg, 5.58 mmol). Attempt at purification by FCC afforded the crude product **184h** as a yellow oil (341 mg, 1.34 mmol, 72% crude yield).

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.5 – 7.4 (m, 1H), 7.3 (tdd, J = 7.3, 5.2, 1.7 Hz, 1H), 7.3 (dt, J = 7.4, 1.7 Hz, 1H), 7.3 – 7.2 (m, 1H), 7.2 (dd, J = 8.7, 2.1 Hz, 2H), 7.0 (dd, J=10.9, 8.4 Hz, 2H), 3.8 (s, 2H), 1.7 (d, J = 0.8 Hz, 3H), 1.4 (9H, s).

HRMS (EI): *m/z* = $[M+H]^{\bullet+}$ calcd for $C_{17}H_{22}NO^{\bullet+}$: 256.1696; found 256.1697.

2-((4-Benzyloxy)phenyl)benzylamine (184i)



$C_{20}H_{19}NO$

M = 289.3780 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188i** (380 mg, 1.33 mmol), LAH (151 mg, 3.99 mmol) and $AlCl_3$ (248 mg, 1.86 mmol). Purification by FCC afforded the product **184i** as a yellow solid (248 mg, 0.857 mmol, 64%).

R_f: 0.23 (DCM/MeOH 1% + NEt_3 1%).

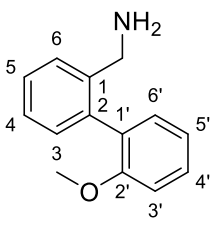
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.47 (dddd, J = 8.9, 8.0, 1.6, 0.8 Hz, 3H, 2''-H and 4''-H and 6''-H), 7.44 – 7.39 (m, 2H, 3''-H and 5''-H), 7.38 – 7.32 (m, 2H, 4-H and 3-H or 5-H), 7.32 – 7.24 (m, 3H, 2'-H and 6'-H and 3-H or 5-H), 7.23 – 7.20 (m, 1H, 6-H), 7.08 – 6.99 (m, 2H, 3'-H and 5'-H), 5.12 (s, 2H, OCH_2), 3.78 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 158.4 (C-4'), 141.6 (C-2), 141.3 (C-1), 137.6 (C-1''), 134.3 (C-1'), 130.6 (C-2' and C-6'), 130.5 (C-6), 128.9 (C-3'' and C-5''), 128.5 (C-3 or C-5), 128.4 (C-3 or C-5), 128.0 (C-2'' and C-6''), 127.7 (C-4), 126.9 (C-4''), 114.9 (C-3' and C-5'), 70.4 (OCH_2), 44.6 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3035, 2916, 2874, 1606, 1576, 1514, 1496, 1387, 1232, 1178, 1117, 1025, 1012, 999, 840, 756, 699.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{20}H_{19}NO^{\bullet+}$: 289.1467; found 289.1462.

2-(2-Methoxyphenyl)benzylamine (184j)



$C_{14}H_{15}NO$

M = 213.2800 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188j** (330 mg, 1.58 mmol), LAH (179 mg, 4.73 mmol) and $AlCl_3$ (294 mg, 2.21 mmol). Purification by FCC afforded the product **184j** as a yellow solid (185 mg, 0.867 mmol, 55%).

R_f: 0.14 (DCM/MeOH 1% + NEt_3 1%).

M.p.: 105 °C.

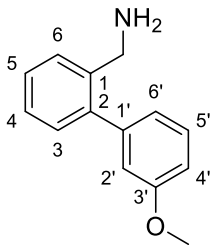
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.47 (ddd, J = 7.5, 1.4, 0.7 Hz, 1H, 6-H), 7.40 – 7.32 (m, 2H, 5-H and 4'-H), 7.27 (td, J = 7.5, 1.5 Hz, 1H, 4-H), 7.18 – 7.10 (m, 2H, 3-H and 6'-H), 7.03 (td, J = 7.4, 1.1 Hz, 1H, 5'-H), 7.01 – 6.98 (m, 1H, 3'-H), 3.76 (s, 3H, OCH_3), 3.59 (d, J = 9.6 Hz, 2H, $C\underline{H_2}NH_2$), 1.46 (2H, s, $CH_2N\underline{H_2}$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 156.9 (C-2'), 142.7 (C-1), 138.1 (C-2), 131.4 (C-3 or C-6'), 130.7 (C-3 or C-6'), 130.4 (C-1'), 129.2 (C-5 and C-4'), 128.0 (C-5 and C-4'), 127.7 (C-6), 126.8 (C-4) , 120.9 (C-5'), 111.1 (C-3'), 55.7 (OCH_3), 44.6 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3360, 3273, 3058, 2961, 2934, 2835, 1711, 1661, 1610, 1514, 1497, 1479, 1433, 1363, 1294, 1233, 1179, 1120, 1021, 1002, 906, 834, 757.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{14}H_{15}NO^{\bullet+}$: 213.1154; found 213.1147.

2-(3-Methoxyphenyl)benzylamine (184k)



$C_{14}H_{15}NO$

M = 213.2800 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188k** (738 mg, 3.52 mmol), LAH (495 mg, 13.0 mmol) and $AlCl_3$ (658 mg, 4.93 mmol). Purification by FCC afforded the product **184k** as a yellow oil (481 mg, 2.26 mmol, 64%).

R_f: 0.15 (DCM/MeOH 1% + NEt_3 1%).

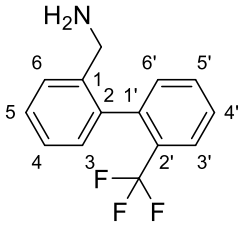
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 7.6 – 7.5 (m, 1H, 6-H), 7.3 (dddd, J = 8.3, 6.2, 3.2, 1.1 Hz, 2H, 5-H and 5'-H), 7.3 (td, J = 7.4, 1.5 Hz, 1H, 4-H), 7.2 (dd, J = 7.6, 1.5 Hz, 1H, 3-H), 7.0 – 6.9 (m, 3H, 2'-H and 4'-H and 6'-H), 3.8 (s, 3H, OCH_3), 3.6 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 159.0 (C-4), 142.3 (C-1), 141.0 (C-1'), 140.4 (C-2), 129.3 (C-3 or C-5 or C-5'), 129.2 (C-3 or C-5 or C-5'), 128.2 (C-6 or C-5 or C-5'), 127.4 (C-5 or C-5'), 126.2 (C-4), 121.3 (C-6' or C-4'), 114.6 (C-2'), 112.6 (C-6' or C-4'), 55.1 (OCH_3), 43.2 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3058, 3001, 2936, 2834, 1596, 1579, 1474, 1421, 1316, 1293, 1210, 1176, 1043, 1019, 860, 784, 756, 702.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{14}H_{15}NO^{\bullet+}$: 213.1154; found 213.1158.

2-[2-(Trifluoromethyl)phenyl]benzylamine (184l)



$C_{14}H_{12}F_3N$

M = 251.2522 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188l** (326 mg, 1.32 mmol), LAH (225 mg, 5.94 mmol) and $AlCl_3$ (246 mg, 1.85 mmol). Purification by FCC afforded the product **184l** as a yellow oil (205 mg, 0.816 mmol, 62%).

R_f: 0.18 (DCM/MeOH 1% + NEt_3 1%).

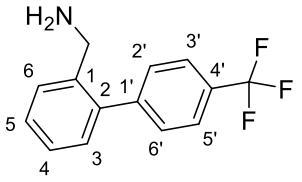
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 7.83 (dd, J = 7.9, 1.3 Hz, 1H, 3'-H), 7.70 (td, J = 7.5, 1.4 Hz, 1H, 5'-H), 7.66 – 7.56 (m, 2H, 6-H and 4'-H), 7.44 – 7.33 (m, 2H, 5-H and 6'-H), 7.25 (td, J = 7.5, 1.3 Hz, 1H, 4-H), 7.07 (d, J = 7.5 Hz, 1H, 3-H), 3.34 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 141.4 (C-1), 139.3 (d, J = 3.1 Hz, C-1'), 137.1 (C-2), 132.1 (C-6), 131.9 (C_{arom}), 128.9 (C_{arom}), 128.0 (d, J = 2.5 Hz, C-5 and C-6'), 127.3 (C-CF_3 or C-2'), 127.0 (C_{arom}), 127.0 (C_{arom}), 125.9 (q, J = 5.2 Hz, C-3') 125.4 (CF_3 or C-2'), 125.3 (C-4), 122.7 (C_{arom}), 43.1 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3342, 3249, 3057, 2925, 2870, 1645, 1601, 1575, 1493, 1429, 1367, 1310, 1259, 1158, 1106, 1068, 1032, 1006, 965, 758, 715.

HRMS (ESI): *m/z* = $[M-H]^-$ calcd for $C_{14}H_{11}F_3N^-$: 250.0849; found 250.0839.

2-[4-(Trifluoromethyl)phenyl]benzylamine (184m)



$C_{14}H_{12}F_3N$

M = 251.2522 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188m** (425 mg, 1.72 mmol), LAH (248 mg, 6.54 mmol) and $AlCl_3$ (321 mg, 2.41 mmol). Purification by FCC afforded the product **184m** as a yellow oil (271 mg, 1.08 mmol, 63%).

R_f: 0.23 (DCM/MeOH 1% + NEt_3 1%).

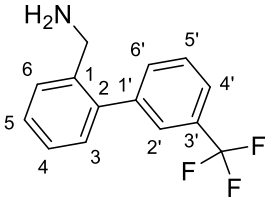
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.71 – 7.66 (m, 2H, 3'-H and 5'-H), 7.49 (tdd, *J* = 7.5, 1.8, 0.9 Hz, 3H, 3-H and 2'-H and 6'-H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H, 4-H), 7.33 (td, *J* = 7.5, 1.5 Hz, 1H, 5-H), 7.22 (dd, *J* = 7.6, 1.5 Hz, 1H, 6-H), 3.79 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 145.0 (C-1'), 140.5 (C-2), 140.0 (C-1), 130.0 (C-6), 129.6 (C-2' and C-6'), 129.4 (d, *J* = 32.3 Hz, CF_3), 128.6 (C-3), 128.4 (C-4), 127.1 (C-5), 125.4 (q, *J* = 3.7 Hz, C-3' and C-5'), 123.0 (C-4'), 44.1 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3339, 3064, 3026, 2860, 1617, 1591, 1468, 1404, 1371, 1321, 1161, 1117, 1104, 1068, 1021, 1006, 842, 765, 756, 745, 711, 657.

HRMS (ESI): *m/z* = $[M-H]^-$ calcd for $C_{14}H_{11}F_3N^-$: 250.0849; found 250.0837.

2-[3-(Trifluoromethyl)phenyl]benzylamine (184n)



$C_{14}H_{12}F_3N$

M = 251.2522 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188n** (445 mg, 1.80 mmol), LAH (205 mg, 5.40 mmol) and $AlCl_3$ (336 mg, 2.52 mmol). Purification by FCC afforded the product **184n** as a yellow oil (302 mg, 1.20 mmol, 67%).

R_f: 0.21 (DCM/MeOH 1% + NEt_3 1%).

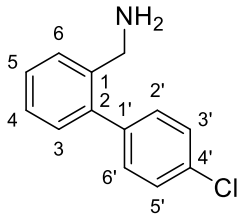
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.69 – 7.62 (m, 2H, 4'-H and 2'-H), 7.62 – 7.54 (m, 2H, 6'-H and 5'-H), 7.54 – 7.50 (m, 1H, 6-H), 7.40 (td, *J* = 7.5, 1.5 Hz, 1H, 5-H), 7.33 (td, *J* = 7.5, 1.5 Hz, 1H, 4-H), 7.24 (dd, *J* = 7.5, 1.5 Hz, 1H, 3-H), 3.75 (s, 2H, $C\underline{H_2}NH_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 142.5 (C-1), 141.0 (C-1'), 140.2 (C-2), 133.1 (C-6' or C-5'), 130.9 (q, *J* = 32.4 Hz, C-3'), 130.3 (C-3), 129.1 (C-5), 128.7 (C-6' or C-5'), 128.7 (C-6), 127.2 (C-4), 126.4 (q, *J* = 3.8 Hz, C-2' or C-4'), 124.2 (d, *J* = 3.9 Hz, C-2' or C-4'), 44.2 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3376, 3292, 3063, 2927, 2870, 1660, 1611, 1592, 1479, 1427, 1331, 1254, 1162, 1118, 1093, 1072, 1024, 905, 805, 757, 705, 657.

HRMS (ESI): *m/z* = $[M-H]^-$ calcd for $C_{14}H_{11}F_3N^-$: 250.0849; found 250.0831.

2-(4-Chlorophenyl)benzylamine (184o)



$C_{13}H_{12}ClN$

M = 217.6960 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188o** (485 mg, 2.27 mmol), LAH (172 mg, 4.54 mmol) and $AlCl_3$ (605 mg, 4.54 mmol). Purification by FCC afforded the product **184o** as a yellow oil (193 mg, 0.887 mmol, 39%):

R_f: 0.23 (DCM/MeOH 1% + NEt_3 1%).

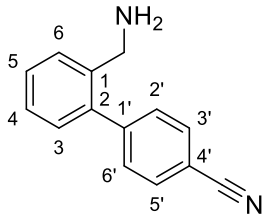
^{1}H NMR (500 MHz, MeOD): δ (ppm) = 7.53 – 7.47 (m, 1H, 6-H), 7.44 (d, J = 8.4 Hz, 2H, 2'-H and 6'-H), 7.38 (td, J = 7.6, 1.5 Hz, 1H, 5-H), 7.35 – 7.27 (m, 3H, 4-H and 3'-H and 5'-H), 7.20 (dd, J = 7.5, 1.5 Hz, 1H, 3-H), 3.72 (s, 2H, C$\underline{H}_2$NH$_2$).

^{13}C NMR (126 MHz, MeOD): δ (ppm) = 141.4 (C-2), 141.2 (C-1'), 140.7 (C-1), 134.3 (C-4'), 131.8 (C-3' and C-5'), 130.9 (C-3), 129.5 (C-2' and C-6'), 129.3 (C-6), 129.2 (C-5), 128.1 (C-4), 43.9 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3370, 3310, 3059, 3024, 2922, 2855, 1591, 1496, 1474, 1445, 1395, 1379, 1088, 1018, 1004, 830, 757, 736.

HRMS (EI): *m/z* [M-H]$^-$ calcd for $C_{13}H_{12}{}^{35}ClN^{\bullet-}$: 216.0586; found 216.0573.

2-(4-Cyanophenyl)benzylamine (184p)



$C_{14}H_{12}N_2$

M = 208.2640 g/mol

This compound was prepared in accordance with **General procedure I** from carbamate **188p** (376 mg, 1.22 mmol) and TFA (2.99 mL, 39.0 mmol). Purification by FCC afforded the product **184p** as a yellow oil (196 mg, 0.941 mmol, 77%).

R_f: 0.14 (DCM/MeOH 1% + NEt_3 1%).

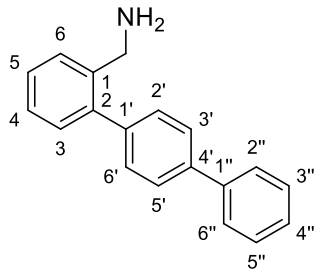
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.7 – 7.7 (m, 2H, 3'-H and 5'-H), 7.6 – 7.5 (m, 3H, 6-H and 2'-H and 6'-H), 7.4 (td, J = 7.5, 1.5 Hz, 1H, 5-H), 7.3 (td, J = 7.5, 1.4 Hz, 1H, 4-H), 7.2 (dd, J = 7.5, 1.5 Hz, 1H, 3-H), 3.7 (s, 2H, C$\underline{H}_2$NH$_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 146.5 (C-1'), 141.0 (C-1), 139.9(C-2), 132.4 (C-3' and C-5'), 130.4 (C-2' and C-6'), 130.0 (C-3), 128.9 (C-5 or C-6), 128.8 (C-5 or C-6), 127.3 (C-4), 119.2 (CF_3), 111.3 (C-4'), 44.2 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3356, 2910, 2360, 2227, 1635, 1590, 1506, 1473, 1373, 1328, 1276, 1180, 1102, 1006, 882, 840, 760, 735.

HRMS (EI): *m/z* = [M]$^{\bullet+}$ calcd for $C_{14}H_{12}N_2{}^{\bullet+}$: 208.1000; found 208.0995.F

[1,1':4',1''-Terphenyl]-2-ylmethanamine (184q)



$C_{19}H_{17}N$

M = 259.3520 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188q** (1.12 g, 4.40 mmol), LAH (668 mg, 17.6 mmol) and $AlCl_3$ (2.34 g, 17.6 mmol). Purification by FCC afforded the product **184q** as a yellow-white solid (1.05 g, 4.05 mmol, 92%).

R_f: 0.23 (DCM/MeOH 1% + NEt_3 1%).

M.p.: 80 – 82 °C.

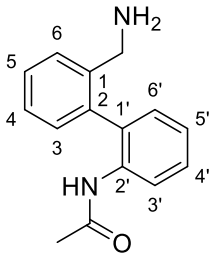
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 7.77 – 7.70 (m, 4H, 2'-H and 6'-H and 2''-H and 6''-H), 7.60 (dd, *J* = 7.6, 1.4 Hz, 1H, 3-H), 7.53 – 7.42 (m, 4H, 3'-H and 5'-H and 3''-H and 5''-H), 7.38 (tdd, *J* = 7.5, 3.6, 1.4 Hz, 2H, 4-H and 4'-H), 7.30 (td, *J* = 7.4, 1.4 Hz, 1H, 5-H), 7.23 (dd, *J* = 7.6, 1.5 Hz, 1H, 6-H), 3.68 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 141.1 (C-2), 140.0 (C-1 or C-1'), 140.0 (C-1 or C-1'), 139.8 (C-4'), 138.7 (C-1''), 129.6 (C-3'' and C-5''), 129.4 (C-6), 129.0 (C-3' and C-5'), 128.3 (C-3), 127.5 (C-4 or C-4'), 127.4 (C-4 or C-4'), 126.6 (C-2'' and C-6''), 126.5 (C-2' and C-6''), 126.3 (C-5), 43.2 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3374, 3026, 2908, 1597, 1475, 1450, 1398, 1336, 1248, 1159, 1004, 880, 847, 749, 697.

HRMS (ESI): *m/z* = $[M-H]^-$ calcd for $C_{19}H_{16}N^-$: 258.1288; found 258.1279.

2-(2-Acetamidophenyl)-benzylamine (184r)



$C_{15}H_{16}N_2O$

M = 240.3060 g/mol

This compound was prepared in accordance with **General procedure I** from carbamate **188r** (511 mg, 1.50 mmol) and TFA (2.99 mL, 39.0 mmol). Purification by FCC afforded the product **184r** as a yellow oil (273 mg, 1.13 mmol, 76%).

R_f: 0.23 (DCM/MeOH 1% + NEt_3 1%).

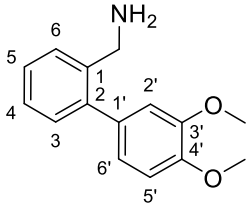
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 10.22 (s, 1H, N<u>H</u>COCH$_3$), 7.59 (d, *J* = 8.0 Hz, 1H, 3'-H), 7.50 (dd, *J* = 7.6, 1.4 Hz, 1H, 6-H), 7.36 (dtd, *J* = 11.5, 7.7, 1.6 Hz, 2H, 5-H and 4'-H), 7.29 (td, *J* = 7.5, 1.5 Hz, 1H, 4-H), 7.21 (td, *J* = 7.4, 1.3 Hz, 1H, 5'-H), 7.14 (dd, *J* = 7.6, 1.7 Hz, 2H, 6'-H), 7.06 (dd, *J* = 7.5, 1.4 Hz, 1H, 3-H), 3.47 (dd, *J* = 100.1, 13.1 Hz, 2H, C<u>H</u>$_2$NH$_2$), 1.79 (s, 3H, NHCOC<u>H</u>$_3$).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 168.1 (NH<u>C</u>OCH$_3$), 140.4 (C-1), 137.9 (C-2), 136.1 (C-2'), 135.3 (C-1'), 130.5 (C-6'), 129.9 (C-3), 128.7 (C-6), 127.8 (C-5), 127.5 (C-4'), 126.6 (C-4), 125.6 (C-3'), 124.7 (C-5'), 43.3 (CH$_2$NH$_2$), 23.1 (NHCO<u>C</u>H$_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3275, 2966, 2361, 2341, 1670, 1581, 1540, 1521, 1474, 1439, 1368, 1301, 1007, 871, 753, 734, 700.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{16}N_2O^{\bullet+}$: 240.1263; found 240.1255.

2-(3,4-Dimethoxyphenyl)benzylamine (184s)



$C_{15}H_{17}NO_2$

M = 243.3060 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188s** (1.44 g, 6.00 mmol), LAH (683 mg, 18.0 mmol) and $AlCl_3$ (2.40 g, 18.0 mmol). Purification by FCC afforded the product **184s** as a yellow oil (793 mg, 3.26 mmol, 54%).

R_f: 0.13 (DCM/MeOH 1% + NEt_3 1%).

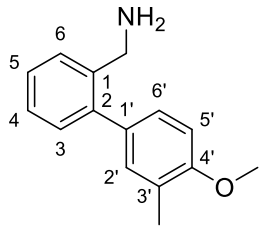
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.45 (ddd, *J* = 7.5, 1.5, 0.6 Hz, 1H, 6-H), 7.33 (td, *J* = 7.5, 1.8 Hz, 1H, 5-H), 7.28 (td, *J* = 7.3, 1.5 Hz, 1H, 4-H), 7.25 – 7.21 (m, 1H, 3-H), 6.94 (d, *J* = 1.6 Hz, 1H, 2'-H), 6.93 (d, *J* = 8.5 Hz, 1H, 5'-H), 6.89 (dd, *J* = 8.2, 1.9 Hz, 1H, 6'-H), 3.87 (s, 3H, 4'-OCH_3), 3.84 (s, 3H, 3'-OCH_3), 3.79 (s, 2H, C$\underline{H_2}$$NH_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 149.2 (C-3'), 148.8 (C-4'), 141.6 (C-1'), 141.5 (C-2), 134.3 (C-1), 130.5 (C-3), 128.5 (C-6), 127.8 (C-5), 126.9 (C-4), 121.6 (C-6'), 113.3 (C-2'), 111.6 (C-5'), 56.2 (3'-OCH_3 or 4'-OCH_3), 56.2 (3'-OCH_3 or 4'-OCH_3), 44.6 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3268, 3015, 2945, 2833, 1600, 1547, 1480, 1486, 1445, 1434, 1254, 1226, 1161, 1008, 1005, 871, 832, 734, 702.

HRMS (ESI): *m/z* = $[M+H]^+$ calcd for $C_{15}H_{18}NO_2^+$: 244.1332; found 244.1332.

2-(4-Methoxy-3-methylphenyl)benzylamine (184t)



$C_{15}H_{17}NO$

M = 227.3070 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188t** (348 mg, 1.56 mmol), LAH (237 mg, 6.24 mmol) and $AlCl_3$ (832 mg, 6.24 mmol). Purification by FCC afforded the product **184t** as a yellow oil (229 mg, 1.01 mmol, 71%).

R_f: 0.14 (DCM/MeOH 1% + NEt_3 1%).

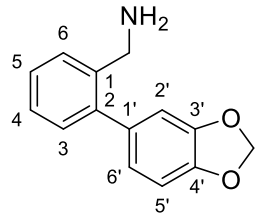
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.48 – 7.39 (m, 1H, 6-H), 7.31 (td, *J* = 7.4, 1.7 Hz, 1H, 5-H), 7.26 (td, *J* = 7.4, 1.6 Hz, 1H, 4-H), 7.21 – 7.18 (m, 1H, 3-H), 7.16 – 7.10 (m, 2H, 2'-H and 6'-H), 6.89 (d, *J* = 8.1 Hz, 1H, 5'-H), 3.87 (s, 3H, OCH_3), 3.77 (s, 2H, C$\underline{H_2}$$NH_2$), 2.25 (s, 3H, CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 157.4 (C-5'), 141.6 (C-1 and C-2), 133.6 (C-1'), 131.8 (C-2' or C-6'), 130.5 (C-3), 128.4 (C-6), 127.8 (C-2' or C-6'), 127.6 (C-5), 126.9 (C-4), 126.6 (C-6'), 110.0 (C-4'), 55.7 (OCH_3), 44.6 (CH_2NH_2), 16.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3364, 3058, 3018, 2920, 2834, 1609, 1589, 1506, 1480, 1463, 1295, 1239, 1170, 1135, 1028, 887, 812, 763, 749, 689.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{17}NO^{\bullet+}$: 227.1310; found 227.1301.

[2-(1,3-Benzodioxol-5-yl)phenyl]methanamine (184u)



$C_{14}H_{13}NO_2$

M = 227.2630 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188u** (317 mg, 1.42 mmol), LAH (216 mg, 5.68 mmol) and $AlCl_3$ (757 mg, 5.68 mmol). Purification by FCC afforded the product **184u** as a yellow oil (246 mg, 1.08 mmol, 76%).

R_f: 0.23 (DCM/MeOH 1% + NEt_3 1%).

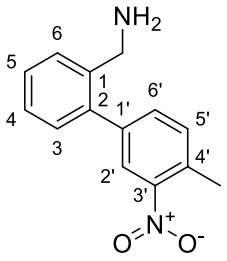
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.45 (ddd, *J* = 7.5, 1.4, 0.6 Hz, 1H, 6-H), 7.32 (td, *J* = 7.4, 1.6 Hz, 1H, 5-H), 7.26 (td, *J* = 7.4, 1.5 Hz, 1H, 4-H), 7.22 – 7.16 (m, 1H, 3-H), 6.87 (dd, *J* = 5.7, 0.5 Hz, 1H, 2'-H), 6.86 (d, *J* = 0.4 Hz, 1H, 5'-H), 6.83 – 6.76 (m, 1H, 6'-H), 6.00 (s, 2H, OCH_2O), 3.77 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 147.9 (C-3'), 147.1 (C-4'), 141.5 (C-1 or C-2), 141.3 (C-1 or C-2), 135.5 (C-1'), 130.5 (C-3), 128.5 (C-6), 127.9 (C-5), 127.0 (C-4), 122.8 (C-6'), 110.1 (C-5'), 108.4 (C-2'), 101.7 (OCH_2O), 44.5 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3348, 3278, 3179, 3056, 3011, 2890, 2848, 2778, 1603, 1591, 1500, 1473, 1450, 1435, 1380, 1335, 1243, 1219, 1104, 1035, 1002, 928, 822, 810, 762, 731.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{13}NO_2^{\bullet+}$: 227.0946; found 227.0941.

2-(4-Methyl-3-nitrophenyl)benzylamine (184v)



$C_{14}H_{14}N_2O_2$

M = 242.2780 g/mol

This compound was prepared in accordance with **General procedure I** from carbamate **188v** (346 mg, 1.01 mmol) and TFA (2.99 mL, 39.0 mmol). Purification by FCC afforded the product **184v** as a yellow oil (240 mg, 0.991 mmol, 98%).

R_f: 0.14 (DCM/MeOH 1% + NEt_3 1%).

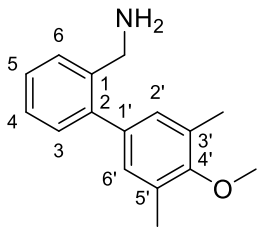
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 8.03 (d, J = 1.9 Hz, 1H, 3-H), 7.56 (dd, J = 7.8, 1.9 Hz, 1H, 6'-H), 7.54 – 7.46 (m, 1H, 6-H), 7.40 (ddd, J = 9.3, 7.5, 1.4 Hz, 2H, 5-H and 5'-H), 7.33 (td, J = 7.4, 1.5 Hz, 1H, 4-H), 7.24 (dd, J = 7.6, 1.5 Hz, 1H, 3-H), 3.77 (s, 2H, $C\underline{H}_2NH_2$), 2.63 (d, J = 0.7 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 149.5 (C-3'), 141.2 (C-1 or C-1'), 140.7 (C-1 or C-1'), 139.2 (C-2), 134.2 (C-6'), 133.0 (C-5'), 132.5 (C-4'), 130.3 (C-3), 128.8 (C-5 or C-6), 128.8 (C-5 or C-6), 127.3 (C-4), 125.5 (C-2'), 44.3 (CH_2NH_2), 20.2 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3377, 3060, 2930, 2865, 2360, 2341, 1558, 1523, 1499, 1443, 1342, 1202, 1158, 1079, 1033, 889, 835, 805, 753, 675.

HRMS (EI): m/z = $[M-H]^{\bullet-}$ calcd for $C_{14}H_{13}N_2O_2^{\bullet-}$: 241.0983; found 241.0973.

2-(4-Methoxy-3,5-dimethylphenyl)benzylamine (184w)



$C_{16}H_{19}NO$

M = 241.3340 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188w** (339 mg, 1.43 mmol), LAH (217 mg, 5.72 mmol) and $AlCl_3$ (763 mg, 5.72 mmol). Purification by FCC afforded the product **184w** as a yellow oil (209 mg, 0.866 mmol, 61%).

R_f: 0.15 (DCM/MeOH 1% + NEt_3 1%).

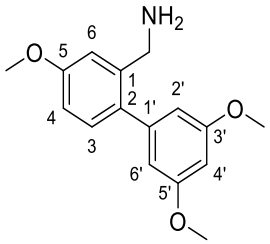
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.48 – 7.41 (m, 1H, 6-H), 7.31 (td, J = 7.5, 1.6 Hz, 1H, 5-H), 7.26 (td, J = 7.4, 1.5 Hz, 1H, 4-H), 7.18 (dd, J = 7.4, 1.6 Hz, 1H, 3-H), 6.97 (s, 2H, 2'-H and 6'-H), 3.77 (s, 2H, $C\underline{H}_2NH_2$), 3.75 (s, 3H, OCH_3), 2.31 (s, 6H, CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 156.6 (C-4'), 141.6 (C-1 or C-2), 141.4 (C-1 or C-2), 137.0 (C-1'), 131.0 (C-3' and C-5'), 130.4 (C-3), 129.9 (C-2' and C-6'), 128.3 (C-6), 127.7 (C-5), 126.8 (C-4), 60.0 (OCH_3), 44.5 (CH_2NH_2), 16.3 (3'-CH_3 and 5'-CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3353, 2922, 2859, 2825, 1588, 1466, 1412, 1371, 1324, 1230, 1199, 1164, 1101, 1077, 1007, 876, 821, 760.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{16}H_{19}NO^{\bullet+}$: 241.1467; found 241.1458.

2-(3,5-Dimethoxyphenyl)-5-methoxybenzylamine (184x)



$C_{16}H_{19}NO_3$

M = 273.332 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **188x** (646 mg, 2.40 mmol), LAH (319 mg, 8.40 mmol), $AlCl_3$ (1.12 g, 8.40 mmol). Purification by FCC afforded the product **184x** as a white-yellow solid (509 mg, 1.89 mmol, 79%).

R_f: 0.15 (DCM/MeOH 1% + NEt_3 1%).

M.p.: 60 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.15 (d, J = 8.4 Hz, 1H, 3-H), 7.02 (d, J = 2.7 Hz, 1H, 6-H), 6.81 (dd, J = 8.4, 2.7 Hz, 1H, 4-H), 6.47 (d, J = 2.3 Hz, 2H, 2'-H and 6'-H), 6.44 (t, J =

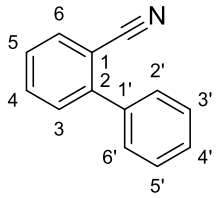
2.1 Hz, 1H, 4'-H), 3.84 (s, 3H, 5'-OCH_3), 3.79 (s, 6H, 3'-OCH_3 and 5'-OCH_3), 3.76 (s, 2H, $C\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 161.1 (C-3' and C-5'), 159.8 (C-5), 143.6 (C-1'), 142.9 (C-1), 134.3 (C-2), 131.3 (C-3), 114.0 (C-6), 112.3 (C-4), 108.1 (C-2' and C-6'), 99.3 (C-4'), 55.9 (3'-OCH_3 and 5'-OCH_3), 55.8 (5'-OCH_3), 44.8 (CH_2NH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3354, 3269, 2955, 2834, 1589, 1455, 1410, 1286, 1227, 1204, 1149, 1063, 818, 702.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{16}H_{19}NO_3^{\bullet+}$: 274.1438; found 274.1439.

2-Phenylbenzonitrile (188)



$C_{13}H_9N$

M = 179.2220 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 1.46 g, 8.00 mmol), phenylboronic acid (**191**, 1.46 g, 12.0 mmol), $Pd(PPh_3)_4$ (462 mg, 0.400 mmol) and Na_2CO_3 (2.54 g, 24.0 mmol). Purification by FCC afforded the product **188** as a white solid (1.32 mg, 7.36 mmol, 92%).

R_f: 0.43 (hexanes/EtOAc 10:1).

M.p.: 37 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.77 (dd, *J* = 7.8, 1.4 Hz, 1H, 6-H), 7.65 (td, *J* = 7.7, 1.4 Hz, 1H, 4-H), 7.57 (dd, *J* = 8.2, 1.6 Hz, 2H, 2'-H and 6'-H or 3'-H and 5'-H), 7.54 – 7.48 (m, 3H, 2'-H and 6'-H and H_{arom} or 3'-H and 5'-H and H_{arom}), 7.48 – 7.42 (m, 2H, H_{arom}).

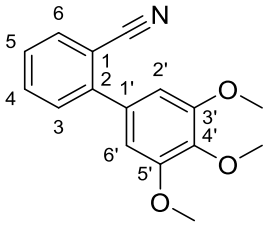
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 145.65 (C-2), 138.28 (C-1'), 133.89 (C-6), 132.94 (C-4), 130.22 (C-5 or C-3 or C-4'), 128.95 – 128.79 (m, C-2' and C-3' and C-5' and C-6' and C_{arom}), 127.67 (C-5 or C-3 or C-4'), 118.85 (CN), 111.45 (C-1).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3062, 3051, 3031, 3017, 2220, 1595, 1475, 1450, 1432, 1270, 1188, 1166, 1075, 1008, 922, 777, 753, 732, 700.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{13}H_9N^{\bullet+}$: 179.0735; found 179.0727.

Literature known compound.[255]

2-(3,4,5-Trimethoxyphenyl)benzonitrile (188a)



$C_{16}H_{15}NO_3$

M = 269.3000 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 278 mg, 1.53 mmol), 3,4,5-trimethoxyphenylboronic acid (**191a**, 357 mg, 1.68 mmol), $Pd(PPh_3)_4$ (88.4 mg, 0.0765 mmol) and Na_2CO_3 (486 mg, 4.59 mmol). Purification by FCC afforded the product **188a** as a white solid (396 mg, 1.47 mmol, 96%).

R_f: 0.24 (hexanes/EtOAc 4:1).

M.p.: 121 – 122 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.77 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H, 6-H), 7.66 (ddd, *J* = 7.9, 7.5, 1.4 Hz, 1H, 4-H), 7.55 (ddd, *J* = 7.9, 1.2, 0.6 Hz, 1H, 3-H), 7.45 (td, *J* = 7.7, 1.4 Hz, 1H, 5-H), 6.79 (s, 2H, 2'-H and 6'-H), 3.90 (s, 6H, 3'-OCH_3 and 5'-OCH_3), 3.84 (s, 3H, 4'-OCH_3).

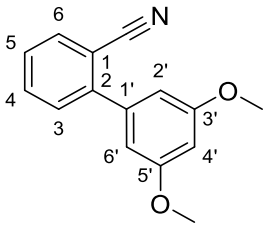
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 154.0 (C-3' and C-5'), 145.9 (C-2), 139.2 (C-4'), 134.3 (C-6), 134.2 (C-1'), 133.3 (C-4), 130.5 (C-3), 128.1 (C-5), 119.3 (CN), 111.8 (C-1), 106.9 (C-2' and C-6'), 61.1 (4'-OCH_3), 56.8 (3'-OCH_3 and 5'-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2224, 1585, 1479, 1410, 1343, 1247, 1126, 1111, 993, 847, 772.

HRMS (EI): m/z $[M]^{\bullet+}$ calcd for $C_{16}H_{15}NO_3^{\bullet+}$ 269.1052; found 269.1046.

Literature known compound.[242]

2-(3,5-Dimethoxyphenyl)benzonitrile (188b)



$C_{15}H_{13}NO_2$

M = 239.2740 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 1.20 g, 6.60 mmol), 3,5-dimethoxyphenylboronic acid (**191b**, 1.80 g, 9.90 mmol), $Pd(PPh_3)_4$ (381 mg, 0.330 mmol) and Na_2CO_3 (1.40 g, 13.2 mmol). Purification by FCC afforded the product **188b** as a white solid (1.39 mg, 5.80 mmol, 88%).

R_f: 0.26 (hexanes/EtOAc 10:1).

M.p.: 93 °C.

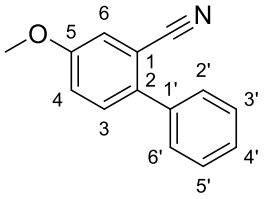
^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.76 (ddd, J = 7.8, 1.4, 0.6 Hz, 1H, 6-H), 7.65 (td, J = 7.7, 1.4 Hz, 1H, 4-H), 7.54 (ddd, J = 7.7, 1.2, 0.5 Hz, 1H, 3-H), 7.46 (td, J = 7.6, 1.3 Hz, 1H, 5-H), 6.68 (d, J = 2.2 Hz, 2H, 2'-H and 6'-H), 6.56 (t, J = 2.3 Hz, 1H, 4'-H), 3.84 (s, 6H, OCH_3).

^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 161.5 (C-3' and C-5'), 145.8 (C-2), 140.8 (C-1'), 134.2 (C-6), 133.3 (C-4), 130.5 (C-3), 128.3 (C-5), 119.1 (CN), 111.8 (C-1), 107.5 (C-2' and C-6'), 101.0 (C-4'), 56.1 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2220, 1607, 1599, 1472, 1420, 1337, 1198, 1160, 1150, 1064, 847, 769, 695.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{13}NO_2^{\bullet+}$: 239.0946; found 239.0930.

5-Methoxy-2-phenylbenzonitrile (188c1)



$C_{14}H_{11}NO$

M = 209.2480 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromo-5-methoxybenzonitrile (**201c**, 848 mg, 4.00 mmol), phenylboronic acid (**191**, 732 mg, 6.00 mmol), $Pd(PPh_3)_4$ (231 mg, 0.200 mmol) and Na_2CO_3 (1.27 g, 12.0 mmol). Purification by FCC afforded the product **188c1** as an off-white solid (803 mg, 3.84 mmol, 96%).

R_f: 0.31 (hexanes/EtOAc 10:1).

M.p.: 85 °C.

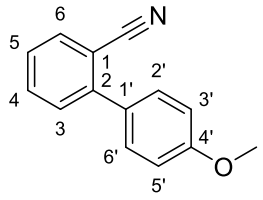
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.56 – 7.52 (m, 2H, 2'-H and 6'-H), 7.51 – 7.44 (m, 3H, 3'-H and 5'-H), 7.44 (d, J = 8.6 Hz, 1H, 3-H), 7.26 (d, J = 2.7 Hz, 1H, 6-H), 7.21 (dd, J = 8.7, 2.7 Hz, 1H, 4-H), 3.87 (s, 3H, OCH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 159.1 (C-5), 138.5 (C-1'), 138.3 (C-2), 131.7 (C-3), 129.2 (C-2' and C-6' or C-3' and C-5'), 129.0 (C-2' and C-6' or C-3' and C-5'), 128.6 (C-4'), 119.9 (C-4), 119.0 (CN), 118.3 (C-6), 112.2 (C-1), 56.2 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2227, 1609, 1562, 1510, 1480, 1440, 1409, 1284, 1268, 1232, 1159, 1116, 1044, 1032, 1003, 913, 875, 825, 761, 726, 692.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}NO^{\bullet+}$: 209.0841; found 209.0834.

2-(4-Methoxyphenyl)benzonitrile (188c2)



$C_{14}H_{11}NO$

M = 209.2480 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 364 mg, 2.00 mmol), 4-methoxyphenylboronic acid (**191c**, 319 mg, 2.10 mmol), $Pd(PPh_3)_4$ (116 mg, 0.100 mmol) and Na_2CO_3 (636 mg, 6.00 mmol). Purification by FCC afforded the product **188c2** as a white solid (404 mg, 1.93 mmol, 97%).

R_f: 0.36 (hexanes/EtOAc 10:1).

M.p.: 84 – 85 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.75 (ddd, *J* = 7.6, 1.4, 0.6 Hz, 1H, 6-H), 7.64 (td, *J* = 7.7, 1.4 Hz, 1H, 4-H), 7.55 – 7.48 (m, 3H, 3-H and 2'-H and 6'-H), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, 5-H), 7.07 – 7.00 (m, 2H, 3'-H and 5'-H), 3.87 (s, 3H, OCH_3).

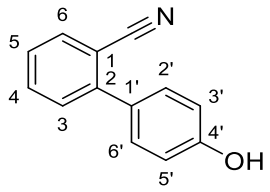
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 160.7 (C-4'), 145.7 (C-2), 134.2 (C-6), 133.3 (C-4), 131.2 (C-1'), 130.6 (C-2' and C-6'), 130.5 (C-3), 127.7 (C-5), 119.4 (CN), 114.6 (C-3' and C-5'), 111.6 (C-1), 55.9 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3066, 2962, 2937, 2837, 2226, 1601, 1498, 1477, 1462, 1431, 1280, 1253, 1235, 1180, 1162, 1124, 1099, 1053, 1024, 1003, 807, 750.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}NO^{\bullet+}$: 209.0841; found 209.0835.

Literature known compound.[256]

2-(4-Hydroxyphenyl)benzonitrile (188e)



$C_{13}H_9NO$

M = 195.2210 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 1.27 g, 6.97 mmol), 4-hydroxyphenylboronic acid (**191e**, 1.32 g, 9.55 mmol), $Pd(PPh_3)_4$ (403 mg, 0.349 mmol) and K_2CO_3 (3.46 g, 20.9 mmol). Purification by FCC afforded the product **188e** as a white solid (982 mg, 5.03 mmol, 72%).

R_f: 0.32 (hexanes/EtOAc 4:1)

M.p.: 179 – 180 °C.

^{1}H NMR (400 MHz, MeOD): δ (ppm) = 7.77 (ddd, *J* = 7.8, 1.4, 0.6 Hz, 1H, 6-H), 7.68 (td, *J* = 7.6, 1.4 Hz, 1H, 4-H), 7.53 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H, 3-H), 7.45 (td, *J* = 7.8, 1.2 Hz, 1H, 5-H), 7.42 – 7.38 (m, 2H, 2'-H and 6'-H), 6.94 – 6.86 (m, 2H, 3'-H and 5'-H).

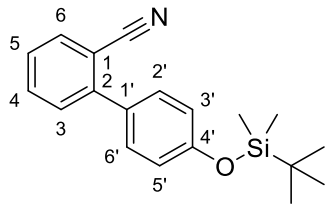
^{13}C NMR (101 MHz, MeOD): δ (ppm) = 159.4 (C-4'), 146.9 (C-2), 134.8 (C-6), 134.2 (C-4), 131.1 (C-2' and C-6'), 131.1 (C-3), 130.8 (C-1'), 128.2 (C-5), 119.9 (CN), 116.5 (C-3' and C-5'), 111.8 (C-1).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3355, 2234, 1613, 1590, 1519, 1478, 1444, 1359, 1279, 1220, 1173, 1101, 825, 754.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{13}H_9NO^{\bullet+}$: 195.0684; found 195.0678.

Literature known compound.[257]

2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)benzonitrile (188f)



$C_{19}H_{23}NOSi$

M = 309.4840 g/mol

This compound was prepared in accordance with **General procedure J** from phenol **188e** (508 mg, 2.60 mmol), imidazole (447 mg, 6.50 mmol) and TBSCl (470 mg, 3.12 mmol). Purification by FCC afforded the product **188f** as a white solid (708 mg, 2.29 mmol, 88%).

R_f: 0.51 (hexanes/EtOAc 10:1).

M.p.: 84 °C.

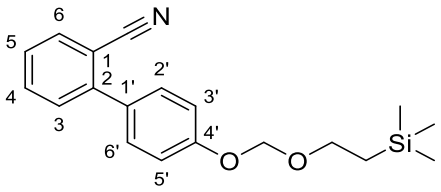
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.75 (ddd, *J* = 7.8, 1.4, 0.6 Hz, 1H, 6-H), 7.64 (td, *J* = 7.7, 1.4 Hz, 1H, 4-H), 7.54 – 7.47 (m, 1H, 3-H), 7.48 – 7.44 (m, 2H, 2'-H and 6'-H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H, 5-H), 7.01 – 6.94 (m, 2H, 3'-H and 5'-H), 1.02 (s, 9H, $C(CH_3)_3$), 0.26 (s, 6H, $Si(CH_3)_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 156.8 (C-4'), 145.5 (C-2), 134.1 (C-6), 133.2 (C-4), 131.7 (C-1'), 130.4 (C-2' and C-6'), 130.3 (C-3), 127.5 (C-5), 120.6 (C-3' and C-5'), 119.2 (CN), 111.4 (C-1), 25.8 ($C(\underline{C}H_3)_3$), 18.5 ($\underline{C}(CH_3)_3$) -4.3 ($Si(\underline{C}H_3)_2$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954, 2854, 2224, 1604, 1510, 1475, 1250, 1171, 1100, 1005, 900, 850, 781, 764.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{19}H_{23}NOSi^{\bullet+}$: 309.1549; found 309.1542.

2-(4-((2-(Trimethylsilyl)ethoxy)methoxy)phenyl)benzonitrile (188g)



$C_{19}H_{23}NO_2Si$

M = 325.4830 g/mol

This compound was prepared in accordance with **General procedure K** from phenol **188e** (264 mg, 1.35 mmol), DIPEA (1.17 mL, 6.75 mmol) and SEMCl (0.717 mL, 4.05 mmol). Purification by FCC afforded the product **188g** as a white solid (249 mg, 0.765 mmol, 57%).

R_f: 0.43 (hexanes/EtOAc 10:1).

M.p.: 81 °C.

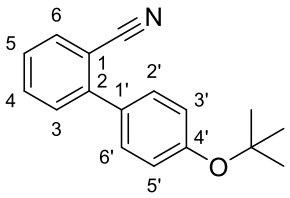
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.75 (ddd, J = 7.8, 1.4, 0.6 Hz, 1H, 6-H), 7.64 (td, J = 7.7, 1.4 Hz, 1H, 4-H), 7.54 – 7.48 (m, 4H, 3-H and 2'-H and 6'-H), 7.43 (td, J = 7.6, 1.2 Hz, 1H, 5-H), 7.20 – 7.13 (m, 2H, 3'-H and 5'-H), 5.28 (s, 2H, OC$\underline{H_2}$O), 3.84 – 3.74 (m, 2H, OC$\underline{H_2}CH_2$), 1.03 – 0.93 (m, 2H, $OCH_2C\underline{H_2}$), 0.02 (s, 9H, $Si(C\underline{H_3})_3$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 158.4 (C-4'), 145.4 (C-2), 134.1 (C-6), 133.2 (C-4), 132.0 (C-1'), 130.4 (C-2' and C-6'), 130.3 (C-3), 127.6 (C-5), 119.2 (CN), 116.7 (C-3' and C-5'), 111.5 (C-1), 93.3 (OCH_2O), 66.8 ($O\underline{C}H_2CH_2$), 18.4 ($OCH_2\underline{C}H_2$), -1.4 ($Si(CH_3)_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2950, 2897, 2224, 1607, 1514, 1477, 1443, 1223, 1178, 1095, 1021, 988, 942, 928, 859, 833, 763, 691.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{19}H_{23}NO_2Si^{\bullet+}$: 325.1498; found 325.1506.

2-(4-(*tert*-Butoxy)phenyl)benzonitrile (188h)



$C_{17}H_{17}NO$

M = 251.3290 g/mol

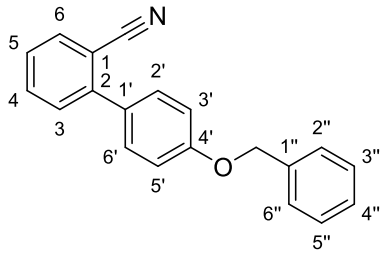
$Mg(ClO_4)_2$ (91.1 mg, 0.410 mmol, 0.100 equiv.) and the phenol **188e** (800 mg, 4.10 mmol, 1.00 equiv.) were dissolved in DCM (20 mL). Then Boc_2O (3.40 g, 15.6 mmol, 3.80 equiv.) was added after which gas evolution was observed. The mixture was stirred at reflux overnight. The crude reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (3 x 10 mL). The organic layer was separated, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Attempt at purification by FCC afforded the crude product **188h** as a colorless oil (477 mg, 1.90 mmol, 46% crude yield).

R_f: 0.51 (hexanes/EtOAc 4:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.8 (ddd, *J* = 7.9, 1.4, 0.6 Hz, 1H), 7.6 (td, *J* = 7.7, 1.4 Hz, 1H), 7.5 (ddd, *J* = 7.9, 1.3, 0.6 Hz, 1H), 7.5 – 7.5 (m, 2H), 7.4 (td, *J* = 7.6, 1.2 Hz, 1H), 7.1 (d, *J* = 8.6 Hz, 1H), 1.4 (s, 9H).

HRMS (EI): *m/z* = $[M-H]^{\bullet-}$ calcd for $C_{17}H_{16}NO^{\bullet-}$: 250.1237; found 250.1239.

2-(4-(Benzyloxy)phenyl)benzonitrile (188i)



$C_{20}H_{15}NO$

M = 285.3460 g/mol

This compound was prepared in accordance with **General procedure L** from phenol **188e** (303 mg, 1.55 mmol), K_2CO_3 (256 mg, 1.55 mmol) and benzyl bromide (298 mg, 1.71 mmol). Purification by FCC afforded the product **188i** as a white solid (423 mg, 1.48 mmol, 96%).

R_f: 0.26 (hexanes/EtOAc 10:1).

M.p.: 100 °C.

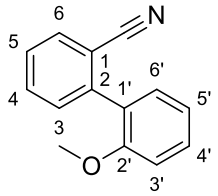
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.75 (ddd, *J* = 7.8, 1.4, 0.6 Hz, 1H, 6-H), 7.64 (td, *J* = 7.7, 1.4 Hz, 1H, 4-H), 7.55 – 7.50 (m, 3H, 2'-H and 6'-H and H_{arom}), 7.50 – 7.46 (m, 2H, H_{arom}), 7.45 – 7.39 (m, 3H, 3''-H and 5''-H and H_{arom}), 7.38 – 7.33 (m, 1H, H_{arom}), 7.15 – 7.08 (m, 2H, 3'-H and 5'-H), 5.14 (s, 2H, OCH_2).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 159.7 (C-5), 145.4 (C-2), 137.3 (C-1'), 134.1 (C-6), 133.2 (C-4), 131.3 (C-1'), 130.5 (C-2' and C-6'), 130.3 (C_{arom}), 129.0 (C-3'' and C-5''), 128.4 (C_{arom}), 128.0 (C-2'' and C-6''), 127.6 (C_{arom}), 119.3 (C_{arom}), 115.3 (C-3' and C-5'), 111.4 (C_{arom}), 70.5 (OCH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3398, 2961, 2910, 2873, 2219, 1716, 1606, 1514, 1467, 1379, 1289, 1238, 1175, 1023, 1011, 999, 828, 764, 745, 700.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{20}H_{15}NO^{\bullet+}$: 285.1154; found 285.1151.

2-(2-Methoxyphenyl)benzonitrile (188j)



$C_{14}H_{11}NO$

M = 209.2480 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 382 mg, 2.10 mmol), 2-methoxyphenylboronic acid (**191j**, 319 mg, 2.10 mmol), $Pd(PPh_3)_4$ (121 mg, 0.105 mmol) and Na_2CO_3 (668 mg, 6.30 mmol). Purification by FCC afforded the product **188j** as a white solid (391 mg, 1.87 mmol, 89%).

R_f: 0.32 (hexanes/EtOAc 10:1).

M.p.: 77 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.73 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H, 6-H), 7.67 – 7.62 (m, 1H, 4-H), 7.48 – 7.42 (m, 4H, 5-H and 4'-H and 3-H), 7.29 – 7.25 (m, 1H, 6'-H), 7.11 – 7.04 (m, 2H, 3'-H and 5'-H), 3.83 (s, 3H, OCH_3).

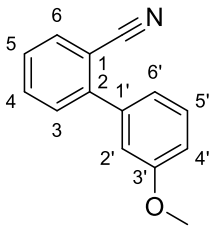
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 157.1 (C-2'), 143.1 (C-2), 133.2 (C-3), 132.9 (C-5), 131.5 (C-5 or C-4'), 131.4 (C-6'), 130.9 (C-4'), 128.0 (C-3 or C-4' or C-5), 128.0 (C-1'), 121.2 (C-3 or C-4' or C-5), 119.0 (CN), 113.9 (C-1), 111.8 (C-3' or C-5'), 56.0 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2993, 2939, 2835, 2223, 1610, 1515, 1479, 1442, 1435, 1299, 1269, 1247, 1183, 1159, 1034, 832, 819, 749.

HRMS (EI): m/z $[M]^{\bullet+}$ calcd for $C_{14}H_{11}NO^{\bullet+}$ 209.0841; found 209.0834.

Literature known compound.[258]

2-(3-Methoxyphenyl)benzonitrile (188k)



$C_{14}H_{11}NO$

M = 209.2480 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 750 mg, 4.12 mmol), 3-methoxyphenylboronic acid (**191k**, 939 mg, 6.18 mmol), $Pd(PPh_3)_4$ (238 mg, 0.206 mmol) and Na_2CO_3 (1.31 g, 12.4 mmol). Purification by FCC afforded the product **188k** as a white solid (787 mg, 3.76 mmol, 91%).

R_f: 0.33 (hexanes/EtOAc 10:1).

M.p.: 63 – 64 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.77 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H, 6-H), 7.66 (td, *J* = 7.7, 1.4 Hz, 1H, 4-H), 7.54 (ddd, *J* = 7.9, 1.3, 0.6 Hz, 1H, 3-H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H, 5-H), 7.42 (dd, *J* = 8.2, 7.7 Hz, 1H, 5'-H), 7.14 (ddd, *J* = 7.6, 1.7, 1.0 Hz, 1H, 6-H), 7.09 (dd, *J* = 2.6, 1.7 Hz, 1H, 2'-H), 7.01 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H, 4'-H), 3.86 (s, 3H, OCH_3).

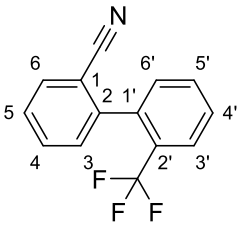
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 160.1 (C-3'), 145.6 (C-2), 140.0 (C-1'), 134.1 (C-6), 133.2 (C-4), 130.4 (C-3), 130.1 (C-5'), 128.1 (C-5), 121.5 (C-6'), 119.0 (CN), 114.8 (C-2'), 114.5 (C-4'), 111.7 (C-1), 55.8 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2938, 2835, 2218, 1603, 1590, 1564, 1470, 1438, 1420, 1308, 1251, 1219, 1188, 1166, 1040, 1019, 994, 864, 780, 760, 741, 693.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}NO^{\bullet+}$: 209.0841; found 209.0835.

Literature known compound.[259]

2-[2-(Trifluoromethyl)phenyl]benzonitrile (188l)



$C_{14}H_8F_3N$

M = 247.2202 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 370 mg, 2.03 mmol), 2-(trifluoromethyl)phenylboronic acid (**191l**, 501 mg, 2.64 mmol), $Pd(PPh_3)_4$ (117 mg, 0.101 mmol) and Na_2CO_3 (645 mg, 6.09 mmol). Purification by FCC afforded the product **188l** as a white solid (400 mg, 1.62 mmol, 80%).

R_f: 0.30 (hexanes/EtOAc 10:1).

M.p.: 64 °C.

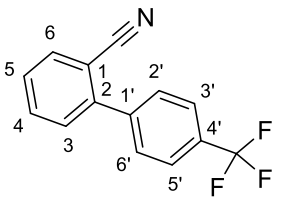
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.83 (ddt, *J* = 7.8, 1.3, 0.7 Hz, 1H, 3'-H), 7.77 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H, 6-H), 7.71 – 7.60 (m, 3H, 4-H and 4'-H and 5'-H), 7.54 (td, *J* = 7.7, 1.2 Hz, 1H, 5-H), 7.43 (ddt, *J* = 7.8, 1.2, 0.7 Hz, 1H, 3-H), 7.39 (ddt, *J* = 7.6, 1.5, 0.7 Hz, 1H, 6'-H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 143.3 (C-2), 137.5 (d, *J* = 1.9 Hz, C-1'), 132.8 (C-6), 132.3 (C-4), 132.2 (C-5'), 131.9 (C-6'), 130.8 (d, *J* = 1.6 Hz, C-3), 129.4 (C-4' or C-5'), 128.9 (C-4' or C-5'), 126.7 (q, *J* = 5.2 Hz, C-3'), 125.7 (C-2' or CF_3), 122.9 (C-2' or CF_3), 117.8 (CN), 113.4 (C-1).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2227, 1595, 1581, 1473, 1439, 1314, 1262, 1173, 1160, 1107, 1069, 1033, 768, 720.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_8F_3N^{\bullet+}$: 247.0609; found 247.0602.

2-[4-(Trifluoromethyl)phenyl]benzonitrile (188m)



$C_{14}H_8F_3N$

M = 247.2202 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 364 mg, 2.00 mmol), 4-(trifluoromethyl)phenylboronic acid (**191m**, 570 mg, 3.00 mmol), $Pd(PPh_3)_4$ (116 mg, 0.100 mmol) and Na_2CO_3 (636 mg, 6.00 mmol). Purification by FCC afforded the product **188m** as a white solid (465 mg, 1.88 mmol, 94%).

R_f: 0.30 (hexanes/EtOAc 10:1).

M.p.: 100 – 101 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.8 (ddd, *J* = 7.8, 1.4, 0.7 Hz, 1H, 6-H), 7.8 – 7.8 (m, 2H, 3'-H and 5'-H), 7.7 – 7.7 (m, 3H, 4-H and 2'-H and 6'-H), 7.6 – 7.5 (m, 2H, 5-H and 3-H).

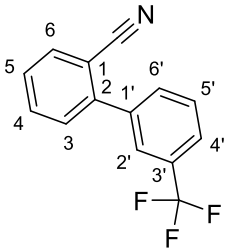
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 143.8 (C-2), 141.9 (C-1'), 133.8 (C-5), 133.1 (C-3), 130.5 (d, *J* = 32.6 Hz, C-4'), 130.1 (C-3), 129.3 (C-2' and C-6'), 128.4 (C-5), 125.6 (q, *J* = 3.9 Hz, C-3' and C-5'), 122.8 (CF_3), 118.2 (CN), 111.3 (C-1).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2225, 1618, 1565, 1480, 1407, 1327, 1269, 1196, 1164, 1102, 1069, 1019, 1006, 842, 765, 733, 708.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_8F_3N^{\bullet+}$: 247.0609; found 247.0602.

Literature known compound.[260]

2-[3-(Trifluoromethyl)phenyl]benzonitrile (188n)



$C_{14}H_8F_3N$

M = 247.2202 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 382 mg, 2.10 mmol), 3-(trifluoromethyl)phenylboronic acid (**191n**, 598 mg, 3.15 mmol), $Pd(PPh_3)_4$ (121 mg, 0.105 mmol) and Na_2CO_3 (668 mg, 6.30 mmol). Purification by FCC afforded the product **188n** as a solid (493 mg, 1.99 mmol, 95%).

R_f: 0.32 (hexanes/EtOAc 10:1).

M.p.: 56 – 57 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.84 – 7.79 (m, 3H, C_{arom}), 7.77 – 7.73 (m, 1H, C_{arom}), 7.70 (dd, J = 7.7, 1.4 Hz, 1H, C_{arom}), 7.69 – 7.64 (m, 1H, C_{arom}), 7.57 – 7.50 (m, 2H, C_{arom}).

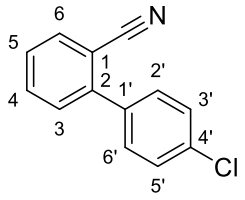
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 144.1 (C_{arom}), 139.5 (C_{arom}), 134.2 (C_{arom}), 133.5 (C_{arom}), 132.8 (C_{arom}), 131.5 (C_{arom}), 131.1 (C_{arom}), 130.5 (C_{arom}), 129.7 (C_{arom}), 128.8 (C_{arom}), 126.1 (q, J = 3.9 Hz, C_{arom}), 125.8 (q, J = 3.9 Hz, C_{arom}), 123.1 (C_{arom}), 118.6 (C_{arom}), 111.8 (C_{arom}).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2961, 2936, 1581, 1508, 1483, 1449, 1408, 1343, 1233, 1171, 1117, 1002, 954, 830, 766, 732.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{14}H_8F_3N^{\bullet+}$: 247.0609; found 247.0605.

Literature known compound.[242]

2-(4-Chlorophenyl)benzonitrile (188o)



$C_{13}H_8ClN$

M = 213.6640 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 482 mg, 2.65 mmol), 4-chlorophenylboronic acid (**191o**, 622 mg, 3.97 mmol), $Pd(PPh_3)_4$ (306 mg, 0.265 mmol) and K_2CO_3 (1.31 g, 7.95 mmol). Purification by FCC afforded the product **188o** as a white solid (540 mg, 2.53 mmol, 95%).

R_f: 0.37 (hexanes/EtOAc 10:1).

M.p.: 114 – 115 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.78 (ddd, J = 7.8, 1.4, 0.6 Hz, 1H, 6-H), 7.68 (td, J = 7.7, 1.4 Hz, 1H, 4-H), 7.54 – 7.49 (m, 5H, H_{arom}), 7.49 – 7.46 (m, 1H, H_{arom}).

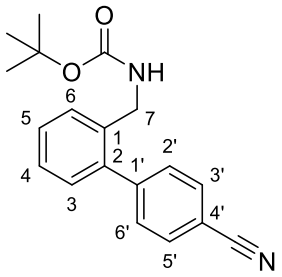
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 144.5 (C-2), 137.2 (C-1' or C-4'), 135.2 (C-1' or C-4'), 134.1 (C-6), 133.4 (C-4), 130.6 (C-2' and C-6' or C-3' and C-5'), 130.4 (C-3 or C-5), 129.3 (C-2' and C-6' or C-3' and C-5'), 128.4 (C-3 or C-5), 111.6 (C-1).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3058, 2923, 2852, 2224, 1593, 1497, 1473, 1440, 1397, 1281, 1090, 1017, 1005, 884, 829, 818, 764, 749, 734.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{13}H_8{}^{35}ClN^{\bullet+}$: 213.0345; found 213.0340.

Literature known compound.[261]

2-(4-Cyanophenyl)-*N*-(*tert*-butoxycarbonyl)benzylamine (188p)



$C_{19}H_{20}N_2O_2$

M = 308.3810 g/mol

This compound was prepared in accordance with **General procedure G** from bromide **217** (572 mg, 2.00 mmol), 4-cyanophenylboronic acid (**191p**, 441 mg, 3.00 mmol), $Pd(PPh_3)_4$ (231 mg, 0.200 mmol) and K_2CO_3 (991 mg, 6.00 mmol). Purification by FCC afforded the product **188p** as a white solid (415 mg, 1.35 mmol, 67%).

R_f: 0.40 (hexanes/EtOAc 4:1).

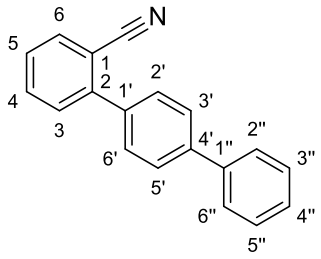
M.p.: 125 °C.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 7.91 (d, *J* = 8.3 Hz, 2H, 3'-H and 5'-H), 7.57 (d, *J* = 8.2 Hz, 2H, 2'-H and 6'-H), 7.45 – 7.40 (m, 2H, 4-H and 5-H), 7.38 – 7.31 (m, 2H, 6-H and $CH_2N\underline{H}$), 7.24 – 7.19 (m, 1H, 6-H), 4.05 (d, *J* = 6.0 Hz, 2H, $C\underline{H}_2NH$), 1.36 (9H, s, $C(C\underline{H}_3)_3$).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 155.62 (NHCOO), 145.30 (C-1'), 138.83 (C-1), 137.02 (C-2), 132.18 (C-3' and C-5'), 130.15 (C-2' and C-6'), 129.40 (C-3), 128.33 (C-5), 127.67 (C-4), 126.94 (C-6), 118.84 (CN), 110.00 (C-4'), 77.83 ($\underline{C}(CH_3)_3$), 41.16 ($\underline{C}H_2NH$), 28.20 ($C(\underline{C}H_3)_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3327, 2961, 2923, 2229, 1687, 1608, 1532, 1477, 1424, 1390, 1365, 1294, 1277, 1254, 1169, 1156, 1050, 961, 942, 885, 849, 771.

[1,1':4',1''-Terphenyl]-2-carbonitrile (188q)



$C_{19}H_{13}N$

M = 255.3200 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 983 mg, 5.40 mmol), 4-biphenylboronic acid (**191q**, 1.60 g, 8.10 mmol), $Pd(PPh_3)_4$ (624 mg, 0.540 mmol) and K_2CO_3 (2.68 g, 16.2 mmol). Purification by FCC afforded the product **188q** as a white solid (1.28 g, 5.02 mmol, 93%).

R_f: 0.35 (hexanes/EtOAc 10:1).

M.p.: 104 – 105 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.80 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H, 6-H), 7.78 – 7.73 (m, 2H, 3'-H and 5'-H), 7.72 – 7.65 (m, 5H, 4-H and 2'-H and 6'-H and 2''-H and 6''-H), 7.59 (ddd, *J* = 7.8, 1.3, 0.6 Hz, 1H, 3-H), 7.54 – 7.44 (m, 3H, 5-H and 3''-H and 5''-H), 7.44 – 7.35 (m, 1H, 4''-H).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 145.3 (C-2), 141.8 (C-4'), 140.6 (C-1''), 137.7 (C-1'), 134.2 (C-6), 133.3 (C-4), 130.5 (C-3), 129.7 (C-3'' and C-5''), 129.3 (C-2' and C-6' or C-2'' and C-6''), 128.1 (d, *J* = 1.9 Hz, C-5 and C-4'), 127.7 (C-2' and C-6' or C-2'' and C-6''), 127.5 (C-3' and C-5'), 119.1 (CN), 111.6 (C-1).

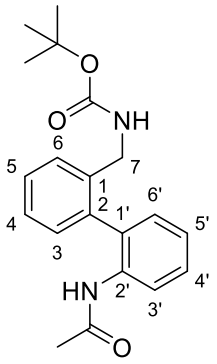
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3064, 3032, 2918, 2849, 2219, 1594, 1475, 1447, 1439, 1399, 1118, 1039, 1004, 844, 759, 740, 696, 680.

HRMS (EI): m/z $[M]^{\bullet+}$ calcd for $C_{19}H_{13}N^{\bullet+}$ 255.1048; found 255.1042.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{19}H_{20}N_2O_2^{\bullet+}$: 308.1525; found 308.1525.

Literature known compound.[262]

2-(2-Acetamidophenyl)-*N*-(*tert*-butoxycarbonyl)benzylamine (188r)



$C_{20}H_{24}N_2O_3$

M = 340.4230 g/mol

This compound was prepared in accordance with **General procedure G** from bromide **217** (572 mg, 2.00 mmol), 2-acetamidophenylboronic acid (**191r**, 537 mg, 3.00 mmol), $Pd(PPh_3)_4$ (231 mg, 0.200 mmol) and K_2CO_3 (991 mg, 6.00 mmol). Purification by FCC afforded the product **188r** as a white solid (467 mg, 1.37 mmol, 69%).

R_f: 0.38 (hexanes/EtOAc 2:1).

M.p.: 62 °C.

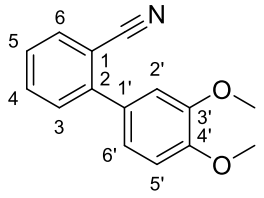
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 8.86 (s, 1H, N<u>H</u>COCH$_3$), 7.59 (dd, *J* = 8.5, 6.2 Hz, 1H, H$_{arom}$), 7.39 – 7.33 (m, 3H, CH$_2$N<u>H</u> and H$_{arom}$), 7.28 (ddd, *J* = 7.6, 5.5, 3.1 Hz, 1H, H$_{arom}$), 7.25 – 7.20 (m, 1H, H$_{arom}$), 7.16 (dd, *J* = 7.6, 1.7 Hz, 1H, H$_{arom}$), 7.04 (d, *J* = 7.5 Hz, 1H, H$_{arom}$), 3.95 – 3.76 (m, 2H, C<u>H</u>$_2$NH), 1.81 (3H, s, NHCOC<u>H</u>$_3$), 1.36 (9H, s, C(C<u>H</u>$_3$)$_3$).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 168.3 (NH<u>C</u>OCH$_3$), 155.9 (<u>C</u>OO), 137.7 (C$_{arom}$), 137.3 (C-2), 134.6 (C$_{arom}$), 130.3 (C$_{arom}$), 129.7 (C$_{arom}$), 127.7 (C$_{arom}$), 126.7 (C$_{arom}$), 126.4 (C$_{arom}$), 125.5 (C$_{arom}$), 125.0 (C$_{arom}$), 77.9 (<u>C</u>(CH$_3$)$_3$), 41.0 (C-7), 28.2 (C(<u>C</u>H$_3$)$_3$), 23.1 (NHCO<u>C</u>H$_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3287, 2931, 2360, 1668, 1622, 1582, 1518, 1442, 1364, 1290, 1250, 1170, 1045, 1007, 933, 860, 755.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{20}H_{24}N_2O_3^{\bullet+}$: 340.1787; found 340.1772.

2-(3,4-Dimethoxyphenyl)benzonitrile (188s)



$C_{15}H_{13}NO_2$

239.2740 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 1.10 g, 6.05 mmol), 3,4-dimethoxyphenylboronic acid (**191s**, 1.32 g, 7.26 mmol), $Pd(PPh_3)_4$ (350 mg, 0.302 mmol) and Na_2CO_3 (1.28 g, 12.1 mmol). Purification by FCC afforded the product **188s** as a white-yellow solid (1.43 g, 5.98 mmol, 99%).

R_f: 0.27 (hexanes/EtOAc 4:1).

M.p.: 141 – 142 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.75 (ddd, J = 7.7, 1.4, 0.6 Hz, 1H, 6-H), 7.64 (td, J = 7.7, 1.4 Hz, 1H, 4-H), 7.53 (ddd, J = 7.9, 1.2, 0.6 Hz, 1H, 3-H), 7.43 (td, J = 7.7, 1.2 Hz, 1H, 5-H), 7.14 (dd, J = 8.2, 2.1 Hz, 1H, 6'-H), 7.10 (d, J = 2.2 Hz, 1H, 2'-H), 7.00 (d, J = 8.3 Hz, 1H, 5'-H), 3.90 (s, 6H, OCH_3).

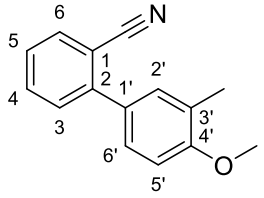
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 150.4 (C-4'), 149.7 (C-3'), 145.8 (C-2), 134.3 (C-6), 133.3 (C-4), 131.4 (C-1'), 130.5 (C-3), 127.7 (C-5), 121.9 (C-6'), 119.5 (CN), 112.9 (C-2'), 112.0 (C-5'), 111.6 (C-1), 56.5 (OCH_3), 56.4 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2219, 1601, 1521, 1481, 1463, 1439, 1333, 1263, 1246, 1217, 1145, 1021, 873, 815, 757.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{13}NO_2^{\bullet+}$: 239.0946; found 239.0943.

Literature known compound.[263]

2-(4-Methoxy-3-methylphenyl)benzonitrile (188t)



$C_{15}H_{13}NO$

M = 223.2750

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 370 mg, 2.03 mmol), 4-methoxy-3-methylphenylboronic acid (**191t**, 521 mg, 3.04 mmol), $Pd(PPh_3)_4$ (235 mg, 0.200 mmol) and K_2CO_3 (1.01 g, 6.09 mmol). Purification by FCC afforded the product **188t** as a white solid (389 mg, 1.74 mmol, 85%).

R_f: 0.39 (hexanes/EtOAc 10:1).

M.p.: 87 °C.

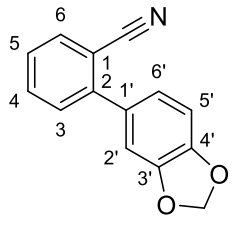
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.74 (ddd, *J* = 7.8, 1.4, 0.6 Hz, 1H, 6-H), 7.63 (td, *J* = 7.7, 1.4 Hz, 1H, 4-H), 7.50 (ddd, *J* = 7.9, 1.3, 0.6 Hz, 1H, 3-H), 7.45 – 7.36 (m, 2H, 5-H and 6'-H), 7.34 – 7.33 (m, 1H, 2'-H), 6.96 (d, *J* = 8.4 Hz, 1H, 4-H), 3.89 (s, 3H, OCH_3), 2.28 (d, *J* = 0.7 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 158.8 (C-4'), 145.8 (C-2), 134.0 (C-6), 133.1 (C-4), 131.3 (C-2'), 130.6 (C-1'), 130.3 (C-3), 127.8 (C-6'), 127.4 (C-3'), 127.4 (C-5), 119.3 (CN), 111.4 (C-1), 110.3 (C-5'), 55.8 (OCH_3), 16.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2220, 1611, 1597, 1512, 1478, 1440, 1304, 1273, 1248, 1140, 1109, 1025, 806, 760.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{13}NO^{\bullet+}$: 223.0997; found 223.0988.

2-(Benzo[*d*][1,3]dioxol-5-yl)benzonitrile (188u)



$C_{14}H_9NO_2$

M = 223.2310 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 366 mg, 2.01 mmol), 4-methoxy-3-methylphenylboronic acid

(**191u**, 511 mg, 3.01 mmol), $Pd(PPh_3)_4$ (232 mg, 0.201 mmol) and K_2CO_3 (996 mg, 6.03 mmol). Purification by FCC afforded the product **188u** as a white solid (357 mg, 1.74 mmol, 87%).

R_f: 0.26 (hexanes/EtOAc 10:1).

M.p.: 96 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.74 (ddd, J = 7.8, 1.4, 0.6 Hz, 1H, 6-H), 7.63 (td, J = 7.7, 1.5 Hz, 1H, 4-H), 7.48 (ddd, J = 7.9, 1.4, 0.6 Hz, 1H, 3-H), 7.43 (td, J = 7.6, 1.2 Hz, 1H, 5-H), 7.05 – 7.03 (m, 1H, 6'-H), 7.03 (s, 1H, 2'-H), 6.97 – 6.91 (m, 1H, 5'-H), 6.05 (s, 3H, OCH_2O).

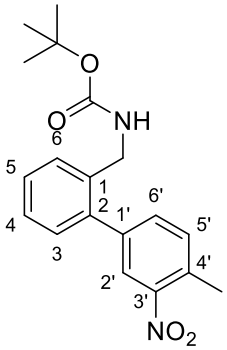
^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 148.6 (C-3' or C-4'), 148.4 (C-3' or C-4'), 145.4 (C-2), 134.1 (C-6), 133.2 (C-4), 132.6 (C-1'), 130.4 (C-3), 127.8 (C-5), 123.2 (C-2'), 119.1 (CN), 111.6 (C-2), 109.5 (C-6'), 108.8 (C-5'), 102.1 (OCH_2O).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3066, 2920, 2223, 1596, 1506, 1478, 1435, 1348, 1285, 1246, 1231, 1108, 1038, 952, 928, 891, 867, 809, 756, 745.

HRMS (EI): m/z $[M]^{\bullet+}$ calcd for $C_{14}H_9NO_2^{\bullet+}$ 223.0633; found 223.0627.

Literature known compound.[264]

2-(4-Methyl-3-nitrophenyl)-*N*-(*tert*-butoxycarbonyl)benzylamine (188v)



$C_{19}H_{21}N_2O_4$

M = 342.3950 g/mol

This compound was prepared in accordance with **General procedure G** from bromide **217** (572 mg, 2.00 mmol), 4-methyl-3-nitrophenylboronic acid (**191v**, 543 mg, 3.00 mmol), $Pd(PPh_3)_4$ (231 mg, 0.200 mmol) and K_2CO_3 (991 mg, 6.00 mmol). Purification by FCC afforded the product **188v** as a white solid (416 mg, 1.21 mmol, 61%).

R_f: 0.46 (hexanes/EtOAc 4:1).

M.p.: 106 °C.

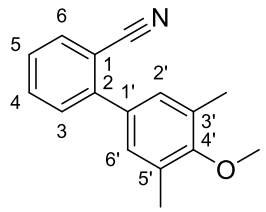
^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.92 (d, *J* = 1.8 Hz, 1H, 2'-H), 7.49 (dd, *J* = 7.8, 1.9 Hz, 1H, 6'-H), 7.45 (dd, *J* = 7.7, 1.6 Hz, 1H, 3-H), 7.42 (d, *J* = 7.8 Hz, 1H, 5'-H), 7.40 (td, *J* = 7.5, 1.5 Hz, 1H, 5-H), 7.36 (td, *J* = 7.4, 1.7 Hz, 1H, 4-H), 7.25 (dd, *J* = 7.4, 1.5 Hz, 1H, 6-H), 4.22 (d, *J* = 5.9 Hz, 2H, C<u>H</u>$_2$NH), 2.63 (s, 3H, CH_3), 1.39 (s, 9H, C(C<u>H</u>$_3$)$_3$).

^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 156.0 (COO), 149.7 (C-3'), 140.4 (C-1), 139.6 (C-1'), 137.0 (C-2), 134.2 (C-6'), 133.3 (C-5'), 132.9 (C-4'), 130.6 (C-6), 129.0 (C-4 or C-5), 128.9 (C-4 or C-5), 128.0 (C-3), 125.5 (C-2'), 79.8 (<u>C</u>(CH$_3$)$_3$), 42.9 (<u>C</u>H$_2$NH), 28.6 (C(<u>C</u>H$_3$)$_3$), 20.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3309, 2979, 2914, 1698, 1681, 1520, 1498, 1452, 1364, 1341, 1294, 1276, 1249, 1158, 1049, 1030, 935, 859, 836, 794, 754.

HRMS (ESI): *m/z* [M-H]$^-$ calcd for $C_{19}H_{21}N_2O_4^-$: 341.1507; found 341.1509.

2-(4-Methoxy-3,5-dimethylphenyl)benzonitrile (188w)



$C_{16}H_{15}NO$

M = 237.3020 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromobenzonitrile (**201**, 377 mg, 2.05 mmol), 3,5-dimethyl-4-methoxyphenylboronic acid (**191w**, 559 mg, 3.07 mmol), $Pd(PPh_3)_4$ (239 mg, 0.205 mmol) and K_2CO_3 (1.03 g, 6.15 mmol). Purification by FCC afforded the product **188w** as a white solid (340 mg, 1.43 mmol, 70%).

R_f: 0.40 (hexanes/EtOAc 10:1).

M.p.: 67 °C.

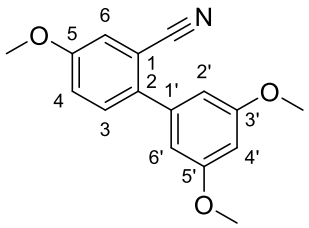
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.74 (ddd, *J* = 7.8, 1.4, 0.6 Hz, 1H, 6-H), 7.66 – 7.60 (m, 1H, 4-H), 7.48 (ddd, *J* = 7.9, 1.3, 0.6 Hz, 1H, 3-H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H, 5-H), 7.21 (d, *J* = 0.6 Hz, 2H, 2'-H and 6'-H), 3.78 (s, 3H, OCH_3), 2.35 (t, *J* = 0.7 Hz, 6H, CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 158.0 (C-4'), 145.7 (C-2), 134.1 (C-1'), 134.0 (C-6), 133.1 (C-4), 131.7 (C-3' and C-5'), 130.4 (C-3), 129.6 (C-2' and C-6'), 127.6 (C-5), 119.2 (CN), 111.5 (C-1), 60.1 (OCH_3), 16.3 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3061, 2919, 2851, 2223, 1572, 1445, 1329, 1235, 1196, 1167, 1113, 999, 892, 858, 756.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{16}H_{15}NO^{\bullet+}$: 237.1154; found 237.1147.

2-(3,5-Dimethoxyphenyl)-5-methoxybenzonitrile (188x)



$C_{16}H_{15}NO_3$

M = 269.3000 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromo-5-methoxybenzonitrile (**201c**, 999 mg, 4.71 mmol), 3,5-dimethoxyphenylboronic acid (**191b**, 1.03 g, 5.65 mmol), $Pd(PPh_3)_4$ (272 mg, 0.236 mmol) and Na_2CO_3 (998 mg, 9.42 mmol). Purification by FCC afforded the product **188x** as a white solid (1.03 g, 3.82 mmol, 81%).

R_f: 0.36 (hexanes/EtOAc 4:1).

M.p.: 83 – 91 °C.

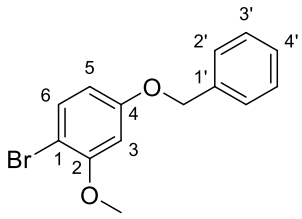
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.45 (dd, *J* = 8.6, 0.5 Hz, 1H, 3-H), 7.25 (m, 1H, 6-H), 7.19 (dd, *J* = 8.7, 2.8 Hz, 1H, 4-H), 6.65 (d, *J* = 2.2 Hz, 2H, 2'-H and 6'-H), 6.52 (t, *J* = 2.3 Hz, 1H, 4'-H), 3.87 (s, 3H, 4-OCH_3), 3.83 (s, 6H, 3'-OCH_3 and 5'-OCH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 160.9 (C-3' and C-5'), 158.8 (C-5), 139.9 (C-1'), 137.7 (C-2), 131.1 (C-3), 119.4 (C-4), 118.5 (C-1), 117.9 (C-6), 111.8 (CN), 106.9 (C-2' and C-6'), 100.0 (C-4'), 55.8 (4-OCH_3), 55.5 (3'-OCH_3 and 5'-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2222, 1738, 1600, 1563, 1500, 1455, 1426, 1407, 1450, 1297, 1276, 1258, 1236, 1205, 1156, 1119, 1064, 1022, 927, 840, 806, 693.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{16}H_{15}NO_3^{\bullet+}$: 269.1052; found 269.1043.

4-(Benzyloxy)-1-bromo-2-methoxybenzene (192)



$C_{14}H_{13}BrO_2$

M = 293.1600 g/mol

This compound was prepared in accordance with **General procedure L** from 4-bromo-3-methoxyphenol (**59**, 5.00 g, 24.6 mmol), benzyl bromide (3.51 mL, 29.5 mmol) and K_2CO_3 (8.14 g, 49.2 mmol) to afford the product **192** as a colorless oil (6.65 g, 22.7 mmol, 92%).

R_f: 0.52 (hexanes/EtOAc 10:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.47 – 7.31 (m, 6H, 2‘-H and 3’-H and 4’-H and 6-H), 6.59 (d, *J* = 2.7 Hz, 1H, 3-H), 6.48 (dd, *J* = 8.7, 2.7 Hz, 1H, 5-H), 5.05 (s, 2H, OCH_2), 3.84 (s, 3H, OCH_3).

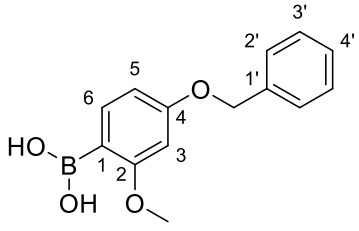
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 160.0 (C-4), 157.2 (C-2), 137.3 (C-1’), 133.6 (C-6), 129.1 (C-3’), 128.7 (C-4’), 128.1 (C-2’), 107.5 (C-5), 103.0 (C-1), 101.3 (C-3), 70.9 (OCH_2), 56.7 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1578, 1486, 1446, 1303, 1279, 1197, 1164, 1054, 1019, 831, 819, 734, 695.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{13}{}^{79}BrO_2{}^{\bullet+}$: 292.0099; found 292.0091.

Literature known compound.[265]

(4-(Benzyloxy)-2-methoxyphenyl)boronic acid (193)



$C_{14}H_{15}BO_4$

M = 258.0800 g/mol

This compound was prepared in accordance with **General procedure M** from *n*-butyllithium (2.5 M in hexanes, 1.07 mL, 11.3 mmol), phenylbromide **192** (3.02 g, 10.3 mmol) and B(O*i*Pr)$_3$ (2.85 mL, 12.4 mmol). Purification by FCC afforded the product **193** as an off-white solid (1.57 g, 6.09 mmol, 59%).

R_f: 0.16 (hexanes/EtOAc 8:1).

M.p.: 99 – 100°C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.72 (d, *J* = 8.2 Hz, 1H 6-H), 7.47 – 7.31 (m, 5H, 2'-H and 3'-H and 4'-H), 6.63 (dd, *J* = 8.3, 2.2 Hz, 5-H), 6.57 (d, *J* = 2.2 Hz, 3-H), 5.70 (s, 2H, $B(OH)_2$), 5.10 (s, 2H, OCH_2), 3.88 (s, OCH_3).

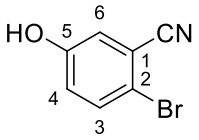
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 166.7 (C-2), 163.5 (C-4), 138.4 (C-6), 137.4 (C-1'), 129.1 (C-2'), 128.6 (C-1 and C-4'), 128.2 (C-3'), 106.7 (C-5), 99.1 (C-3), 70.6 (OCH_2), 56.1 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3340, 1588, 1452, 1289, 1254, 1200, 1149, 1040, 1016, 823, 758, 731, 721, 689.

HRMS (EI): *m/z* = $[M–B(OH)_2]^{\bullet+}$ calcd for $C_{14}H_{14}O_2^{\bullet+}$: 214.0994; found 214.0989.

Literature known compound.[266]

2-Bromo-5-hydroxybenzonitrile (195)



C_7H_4BrNO

M = 198.0190 g/mol

3-Hydroxybenzonitrile (**194**, 2.50 g, 21.0 mmol, 1.00 equiv.) was dissolved in MeCN (20.0 mL) and cooled to -20 °C. $BF_3{\cdot}OEt_2$ (2.59 mL, 21.0 mmol, 1.00 equiv.) followed by NBS (3.74 g, 21.0 mmol, 1.00 equiv.) were added and the mixture allowed to warm to ambient temperature. The resulting mixture was stirred at this temperature for 12 h, then treated with aqueous NH_4Cl solution (0.10 L) and H_2O (0.10 L) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration,

the solvent was removed *in vacuo*. Purification by FCC afforded the product **195** as a light-yellow solid (2.13 g, 10.8 mmol, 51 %).

R_f: 0.29 (hexanes/EtOAc 4:1).

M.p.: 181 – 182 °C.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 10.49 (1H, s, OH), 7.63 (d, J = 8.9 Hz, 1H, 3-H), 7.24 (d, J = 2.9 Hz, 1H, 6-H), 7.04 (dd, J = 8.9, 3.0 Hz, 1H, 4-H).

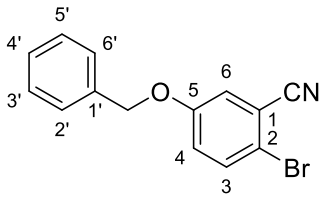
^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 157.1 (C-5), 134.2 (C-3), 122.6 (C-4), 120.9 (C-6), 117.2 (C-2), 114.8 (C-1), 112.6 (CN).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3344, 3101, 2237, 1591, 1487, 1472, 1427, 1304, 1232, 1173, 1125, 964, 860. 836, 785, 691.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_7H_4{}^{79}BrNO^{\bullet+}$: 196.9476; found 196.9472.

Literature known compound.[267]

5-(Benzyloxy)-2-bromobenzonitrile (196)



$C_{14}H_{10}BrNO$

M = 288.1440 g/mol

This compound was prepared in accordance with **General procedure L** from 2-bromo-5-hydroxybenzonitrile (**195**, 4.88 g, 24.6 mmol), benzyl bromide (3.51 mL, 29.5 mmol) and K_2CO_3 (6.81 g, 49.2 mmol) to afford the product **196** as a white solid (4.29 g, 14.9 mmol, 61%).

R_f: 0.50 (hexanes/EtOAc 5:1).

M.p.: 98 – 99 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.57 (d, J = 8.9 Hz, 1H, 3-H), 7.44 – 7.35 (m, 5H, 2'-H, 3'-H, 4'-H, 5'-H and 6'-H), 7.25 (d, J = 3.0 Hz, 1H, 6-H), 7.10 (dd, J = 9.0, 3.0 Hz, 1H, 4-H), 5.07 (s, 2H, OCH_2).

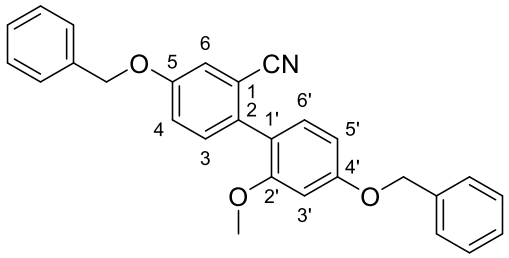
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 158.4 (C-5), 134.6 (C-3), 131.0 (C-1'), 129.3 (C-3' and C-5'), 129.0 (C-4'), 128.1 (C-2' and C-6'), 122.2 (C-4), 120.6 (C-6), 117.6 (C-2), 116.7 (C-1), 116.2 (C-7), 71.3 (OCH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2232, 1590, 1473, 1457, 1388, 1318, 1306, 1242, 1168, 1130, 1003, 946, 913, 870, 835, 735, 715, 694.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{10}{}^{79}BrNO^{\bullet+}$: 286.9946; found 286.9954.

Literature known compound.[268]

5-Benzyloxy-2-(2-methoxy-4-(benzyloxy)phenyl)benzonitrile (197)



$C_{28}H_{23}NO_3$

M = 421.4960 g/mol

This compound was prepared in accordance with **General procedure G** from phenyl bromide **196** (444 mg, 1.54 mmol), boronic acid **193** (5.96 mg, 2.31 mmol), $Pd(PPh_3)_4$ (89.0 mg, 0.0770 mmol) and K_2CO_3 (509 mg, 3.08 mmol) to afford the product **197** as an off-white solid (552 mg, 1.31 mmol, 85%).

R_f: 0.5 (hexanes/EtOAc 6:1).

M.p.: 173 – 174 °C.

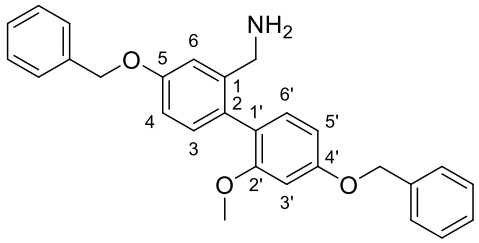
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.48 – 7.44 (m, 2H, H_{benzyl}), 7.44 – 7.40 (m, 6H, H_{benzyl}), 7.37 (ddd, *J* = 5.7, 4.8, 2.1 Hz, 2H, H_{benzyl}), 7.34 (d, *J* = 8.7 Hz, 1H, 6-H), 7.28 (d, *J* = 2.7 Hz, 1H, 3-H), 7.21 (dd, *J* = 8.6, 2.7 Hz, 1H, 4-H), 7.16 (d, *J* = 8.1 Hz, 1H, 6'-H), 6.67 – 6.63 (m, 2H, 3'-H and 5'-H), 5.10 (bs, 4H, OCH_2), 3.80 (s, 3H, OCH_3).

^{13}C NMR (400 MHz, CD_2Cl_2): δ (ppm) = 160.7 (C-4'), 157.8 (C-2'), 157.5 (C-5), 136.9 (C_{benzyl}), 136.2 (C_{benzyl}), 135.2 (C-2), 132.5 (C-6), 131.7 (C-6'), 128.9 (C_{benzyl}), 128.8 (C_{benzyl}), 128.5 (C_{benzyl}), 128.3 (C_{benzyl}), 127.8 (C_{benzyl}), 127.6 (C_{benzyl}), 120.1 (C-1'), 119.9 (C-4), 118.8 (C-1), 118.3 (C-3), 114.1 (CN), 105.7 (C-3' or C-5'), 100.0 (C-3' or C-5'), 70.6 (OCH_2), 70.4 (OCH_2), 55.6 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2924, 1600, 1490, 1453, 1381, 1308, 1272, 1253, 1192, 1160, 1121, 1019, 993, 948, 822, 759, 698.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{28}H_{23}NO_3^{\bullet+}$: 421.1678; found 421.1676.

5-Benzyloxy-2-(2-methoxy-4-(benzyloxy)phenyl)benzylamine (198)



$C_{28}H_{27}NO_3$

M = 425.5280 g/mol

This compound was prepared in accordance with **General procedure H** from benzonitrile **197** (400 mg, 0.950 mmol), LAH (152 mg, 4.01 mmol) and $AlCl_3$ (520 mg, 3.90 mmol) to afford the product **198** as a yellow solid (288 mg, 0.677 mmol, 71%).

R_f: 0.25 (hexanes/EtOAc 1:1 + 1% NEt_3).

M.p.: 161 – 162 °C.

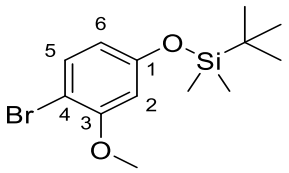
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.50 – 7.46 (m, 4H, H_{arom}), 7.45 – 7.38 (m, 4H, H_{arom}), 7.38 – 7.32 (m, 2H, H_{arom}), 7.11 (d, *J* = 2.7 Hz, 1H, 6-H), 7.06 – 6.99 (m, 2H, H_{arom}), 6.86 (1H, dd, *J* = 8.4, 2.7 Hz, 4-H), 6.65 – 6.59 (m, 2H, 3-H and H_{arom}), 5.11 (s, 2H, 4'-OCH_2 or 5-OCH_2), 5.10 (s, 2H, 4'-OCH_2 or 5-OCH_2), 3.73 (s, 3H, OCH_3), 3.56 (s, C$\underline{H}_2NH_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 160.1 (C-4'), 158.9 (C-5), 158.3 (C-2), 144.8 (C_{arom}), 138.0 (C_{arom}), 137.8 (C_{arom}), 132.2 (C_{arom}), 132.2 (C_{arom}), 130.5 (C_{arom}), 129.1 (C_{arom}), 129.1 (C_{arom}), 128.6 (C_{arom}), 128.5 (C_{arom}), 128.2 (C_{arom}), 128.1 (C_{arom}), 123.1 ($C_{quaternary}$), 114.2 (C-4'), 112.9 (C-4), 105.7 (C_{arom}), 99.8 (C_{arom}), 70.7 (4'-OCH_2 or 5-OCH_2), 70.5 (4'-OCH_2 or 5-OCH_2), 55.9 (OCH_3), 44.9 (CH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2930, 1598, 1452, 1381, 1301, 1234, 1166, 1017, 996, 821, 758, 699.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{28}H_{27}NO_3^{\bullet+}$: 425.1991; found 425.1980.

(4-Bromo-3-methoxyphenoxy)(*tert*-butyl)dimethylsilane (204)



$C_{13}H_{21}BrO_2Si$

M = 317.2980 g/mol

This compound was prepared in accordance with **General procedure J** from phenol **59** (8.33 g, 41.0 mmol), imidazole (6.98 g, 103 mmol) and TBSCl (8.65 g, 57.4 mmol). Purification by FCC afforded the product **204** as a colorless oil (12.6 g, 39.8 mmol, 97%).

R_f: 0.51 (hexanes/EtOAc 20:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.33 (d, J = 8.5 Hz, 1H, 5-H), 6.44 (d, J = 2.6 Hz, 1H, 2-H), 6.36 (dd, J = 8.5, 2.6 Hz, 1H, 6-H), 3.83 (s, 3H, OCH_3), 0.98 (s, 9H, $C(CH_3)_3$), 0.21 (s, 6H, $Si(CH_3)_2$).

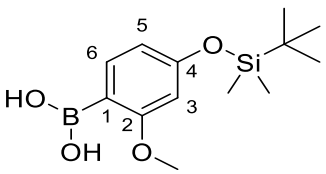
^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 157.1 (C-1 or C-3), 157.0 (C-1 or C-3), 133.5 (C-5), 113.8 (C-6), 105.7 (C-2), 103.4 (C-4), 56.6 (OCH_3), 26.0 ($C(\underline{C}H_3)_3$), 18.6 ($\underline{C}(CH_3)_3$), -4.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2955, 2930, 2886, 2858, 1587, 1484, 1471, 1463, 1447, 1403, 1298, 1254, 1202, 1168, 1051, 975, 834, 778, 703, 669.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{13}H_{21}{}^{79}BrO_2Si^{\bullet+}$: 316.0494; found 316.0499.

Literature known compound.[269]

(4-((*tert*-Butyldimethylsilyl)oxy)-2-methoxyphenyl)boronic acid (205)



$C_{13}H_{23}BO_4Si$

M = 282.2180 g/mol

This compound was prepared in accordance with **General procedure M** from *n*-butyllithium (2.5 M in hexanes, 17.2 mL, 43.0 mmol, 1.10 equiv.), phenylbromide **204** (12.4 g, 39.1 mmol,

1.00 equiv.) and $B(O^iPr)_3$ (11.0 mL, 46.9 mmol, 1.20 equiv.) Purification by FCC afforded the product **205** as an off-white solid (7.23 g, 25.6 mmol, 66%).

R_f: 0.37 (hexanes/EtOAc 4:1).

M.p.: 124 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.21 (d, J = 8.1 Hz, 1H, 6-H), 6.07 (dd, J = 8.1, 2.0 Hz, 1H, 5-H), 5.99 (d, J = 2.0 Hz, 1H, 3-H), 5.32 (s, 2H, $B(OH)_2$), 3.43 (s, 3H, OCH_3), 0.56 (s, 9H, $C(CH_3)_3$), -0.20 (6H, s, $Si(CH_3)_2$) .

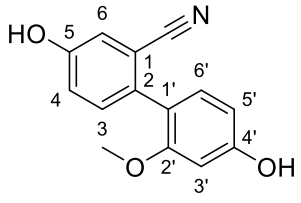
^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 166.6 (C-2), 160.5 (C-4), 137.9 (C-6), 113.0 (C-1 and C-5), 103.3 (C-3), 55.8 (OCH_3), 25.8 ($C(\underline{C}H_3)_3$), 18.5 ($\underline{C}(CH_3)_3$), -4.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3356, 3200, 2957, 2928, 2856, 1597, 1561, 1455, 1418, 1361, 1340, 1293, 1253, 1205, 1157, 1109, 1082, 1039, 979, 838, 777, 664.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{13}H_{23}BO_4Si^{\bullet+}$: 282.1459; found 282.1448.

Literature known compound.[270]

5-Hydroxy-2-(2-methoxy-4-hydroxyphenyl)benzonitrile (206)



$C_{14}H_{11}NO_3$

M = 241.2460 g/mol

This compound was prepared in accordance with **General procedure G** from phenylbromide **195** (3.25 g, 16.4 mmol), boronic acid **205** (7.22 g, 1.56 mmol), $Pd(PPh_3)_4$ (948 mg, 0.820 mmol) and K_2CO_3 (8.13 g, 49.2 mmol). Purification by FCC afforded the product **206** as a white solid (1.61 g, 6.67 mmol, 41%).

R_f: 0.30 (hexanes/EtOAc 1:1).

M.p.: 234 °C.

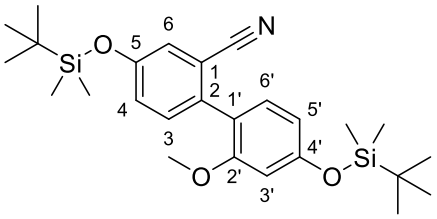
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 9.87 (s, 2H, 5-OH and 4'-OH), 7.21 (d, J = 8.4 Hz, 1H, 3-H), 7.11 (d, J = 2.5 Hz, 1H, 6-H), 7.07 (dd, J = 8.4, 2.6 Hz, 1H, 4-H), 6.98 (d, J = 8.2 Hz, 1H, 6'-H), 6.50 (d, J = 2.2 Hz, 1H, 3'-H), 6.43 (dd, J = 8.2, 2.2 Hz, 1H, 5'-H), 3.68 (s, 3H, OCH_3).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 159.0 (C-4'), 157.3 (C-2'), 156.2 (C-5), 133.0 (C-2), 132.4 (C-3), 131.3 (C-6'), 120.3 (C-4), 118.6 (C-1'), 118.4 (C-6), 117.7 (CN), 112.9 (C-1), 107.2 (C-5'), 99.3 (C-3'), 55.1 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3329, 3255, 2929, 2233, 1606, 1594, 1471, 1442, 1364, 1214, 1293, 1222, 1194, 1165, 1129, 1035, 960, 946, 852, 830, 822, 800.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}NO_3^{\bullet+}$: 241.0739; found 241.0741.

4,4'-Bis((*tert*-butyldimethylsilyl)oxy)-2'-methoxy-[1,1'-biphenyl]-2-carbonitrile (207)



$C_{26}H_{39}NO_3Si_2$

M = 469.7720 g/mol

This compound was prepared in accordance with **General procedure J** from diphenol **206** (1.61 g, 6.67 mmol), TBSCl (2.81 g, 18.7 mmol) and imidazole (2.27 g, 33.4 mmol). Purification by FCC afforded the product **207** as a clear oil (2.73 mg, 5.81 mmol, 87%).

R_f: 0.52 (hexanes/EtOAc 10:1).

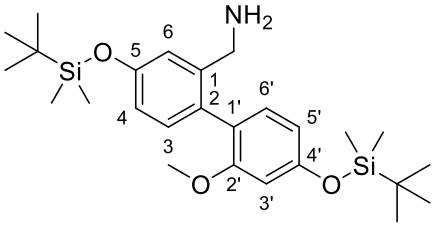
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.28 (d, *J* = 8.5 Hz, 1H, 3-H), 7.15 (d, *J* = 2.6 Hz, 1H, 6-H), 7.11 – 7.05 (m, 2H, 2'-H and 4-H), 6.53 (d, *J* = 7.2 Hz, 2H, 3'-H and 5'-H), 3.78 (s, 3H, OCH_3), 1.02 (s, 9H, 5-$(CH_3)_3$ or 4'-$C(CH_3)_3$), 1.01 (s, 9H, 5-$(CH_3)_3$ or 4'-$C(CH_3)_3$), 0.26 (s, 6H, 5-$Si(CH_3)_2$ or 4'-$Si(CH_3)_2$), 0.25 (s, 6H, 5-$Si(CH_3)_2$ or 4'-$Si(CH_3)_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 158.2 (C-6'), 158.0 (C-4'), 155.0 (C-5), 136.0 (C-2), 132.9 (C-3), 131.9 (C-4 or C-6'), 125.1 (C-4 or C-6'), 124.2 (C-6), 120.9 (C-1'), 119.0 (CN), 114.5 (C-1), 112.3 (C-3' or C-5'), 104.5 (C-3' or C-5'), 55.9 (OCH_3), 26.0 (5-$C(\underline{C}H_3)_3$ or 4'-$(CH_3)_3$), 25.9 (5-$C(\underline{C}H_3)_3$ or 4'-$(CH_3)_3$), 18.7 (5-$\underline{C}(CH_3)_3$ or 4'-$\underline{C}(CH_3)_3$), 18.6 (5-$\underline{C}(CH_3)_3$ or 4'-$\underline{C}(CH_3)_3$), -4.1 (5-$Si(CH_3)_2$ or 4'-$Si(CH_3)_2$), -4.2 (5-$Si(CH_3)_2$ or 4'-$Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2957, 2929, 2885, 2857, 2234, 1602, 1577, 1482, 1472, 1461, 1444, 1407, 1284, 1252, 1198, 1161, 1037, 976, 832, 777, 679.

HRMS (ESI): *m/z* = $[M+H]^+$ calcd for $C_{26}H_{40}NO_3Si_2^+$: 470.2547; found 470.2545.

(4,4'-Bis((*tert*-butyldimethylsilyl)oxy)-2'-methoxy-[1,1'-biphenyl]-2-yl)methanamine (208)



$C_{26}H_{43}NO_3Si_2$

M = 473.8040 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **207** (2.73 g, 5.81 mmol), LAH (882 mg, 23.2 mmol) and $AlCl_3$ (3.10 g, 23.2 mmol). Purification by FCC afforded the product **208** as a white solid (2.20 g mg, 4.64 mmol, 80%).

R_f: 0.15 (DCM/MeOH 1% + NEt_3 1%).

M.p.: 98 °C.

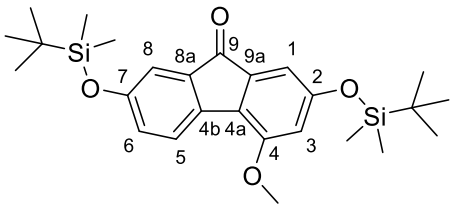
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 6.97 (d, J = 8.2 Hz, 1H, 3-H), 6.94 (dd, J = 7.6, 0.7 Hz, 1H, 1-H), 6.92 (d, J = 2.6 Hz, 1H, 6-H), 6.72 (dd, J = 8.2, 2.6 Hz, 1H, 4-H), 6.48 (d, J = 7.7 Hz, 2H, 3'-H and 5'-H), 3.71 (s, 3H, OCH_3), 3.51 (s, 2H, 5-Si$(CH_3)_2$ or 4'-Si$(CH_3)_2$), 1.01 (d, J = 0.9 Hz, 18H, 5-C$(CH_3)_3$ and 4'-C$(CH_3)_3$), 0.25 (d, J = 2.6 Hz, 12H, 5-Si$(CH_3)_2$ or 4'-Si$(CH_3)_2$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 157.5 (C-2'), 156.2 (C-4'), 155.1 (C-5), 144.2 (C-1), 131.5 (C-3 or C-6'), 131.5 (C-3 or C-6'), 130.4 (C-2), 122.8 (C-1'), 118.6 (C-6), 117.5 (C-4), 111.5 (C-3' or C-5'), 103.4 (C-3' or C-5'), 55.3 (OCH_3), 44.3 (CH_2NH_2), 25.4 (5-C$(CH_3)_3$ and 4'-C$(CH_3)_3$), 18.1 (d, J = 2.9 Hz, 5-C$(CH_3)_3$ and 4'-C$(CH_3)_3$), -4.7 (d, J = 1.3 Hz, 5-Si$(CH_3)_2$ and 4'-Si$(CH_3)_2$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2956, 2928, 2893, 2858, 1600, 1568, 1472, 1460, 1404, 1276, 1251, 1196, 1160, 1116, 1034, 973, 836, 774.

HRMS (ESI): m/z = $[M+H]^+$ calcd for $C_{26}H_{44}NO_3Si_2^+$: 474.2860; found 474.2858.

2,7-Bis((*tert*-butyldimethylsilyl)oxy)-4-methoxy-9*H*-fluoren-9-one (209)



$C_{26}H_{38}O_4Si_2$

M = 470.7560 g/mol

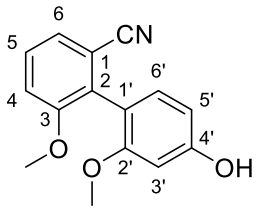
This compound was prepared in accordance with **General procedure A1** from amine **208** (929 mg, 1.96 mmol) and aqueous TBHP (70%, 0.760 mL, 7.84 mmol). Purification by FCC proved difficult. The crude compound mixture **209** (777 mg) was used in the next reaction without further purification.

R_f: 0.56 (hexanes/EtOAc 10:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.54 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.02 (dd, *J* = 2.4, 0.5 Hz, 1H), 6.87 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.69 (d, *J* = 1.9 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 3.91 (s, 3H), 1.00 (s, 9H), 0.99 (s, 9H), 0.24 (s, 6H), 0.21 (s, 6H).

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{26}H_{38}O_4Si_2^{\bullet+}$: 470.2309; found 471.2384.

3-Methoxy-2-(2-methoxy-4-hydroxyphenyl)benzonitrile (211)



$C_{15}H_{13}NO_3$

M = 255.2730 g/mol

This compound was prepared in accordance with **General procedure G** from 2-chloro-3-methoxybenzonitrile (**210**, 335 mg, 2.00 mmol, 1.00 equiv.), boronic acid **205** (564 mmol, 2.00 mmol, 1.00 equiv.), $Pd(OAc)_2$ (67.4 mg, 0.300 mmol, 0.150 equiv.), Sphos (123 mg, 0.300 mmol, 0.150 equiv.) and K_2CO_3 (991 mg, 6.00 mmol, 3.00 equiv.). Purification by FCC afforded the product **211** as a red-brown oil (364 mg, 1.43 mmol, 71%).

R_f: 0.62 (hexanes/EtOAc 1:1).

M.p.: 181 – 182 °C.

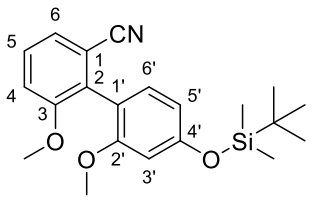
^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ (ppm) = 8.55 (bs, 1H, OH), 7.46 (dd, J = 8.5, 7.5 Hz, 1H, 5-H), 7.36 – 7.32 (m, 2H, 4-H and 6-H), 7.00 (d, J = 8.2 Hz, 1H, 6'-H), 6.60 (d, J = 2.2 Hz, 1H, 3'-H), 6.52 (dd, J = 8.2, 2.3 Hz, 1H, 5'-H), 3.77 (s, 3H, 2'-OCH_3), 3.72 (s, 3H, 3-OCH_3).

^{13}C NMR (101 MHz, $CD_3)_2CO$): δ (ppm) = 160.1 (C-4'), 159.2 (C-3), 158.8 (C-2'), 132.7 (C-6'), 132.7 (C-2), 129.8 (C-5), 125.0 (C-4), 118.9 (CN), 116.5 (C-6), 116.0 (C-1), 115.8 (C-1'), 107.8 (C-5'), 100.2 (C-3'), 56.3 (2'-OCH_3), 55.7 (3-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3312, 2241, 1616, 1589, 1515, 1463, 1428, 1299, 1265, 1198, 1162, 1130, 1068, 1033, 953, 844, 792, 746, 678.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{13}NO_3^{\bullet+}$: 255.0895; found 255.0894.

3-Methoxy-2-(2-methoxy-4-((*tert*-butyldimethylsilyl)oxy)phenyl)benzonitrile (212)



$C_{21}H_{27}NO_3Si$

M = 369.5360 g/mol

This compound was prepared in accordance with **General procedure J** from phenol **211** (408 mg, 1.60 mmol), TBSCl (458 mg, 3.04 mmol) and imidazole (272 mg, 4.00 mmol). Purification by FCC afforded the product **212** as a white solid (479 mg, 1.41 mmol, 88%).

R_f: 0.40 (hexanes/EtOAc 8:1).

M.p.: 104 – 105 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.39 (dd, J = 8.3, 7.7 Hz, 1H, 5-H), 7.30 (dd, J = 7.7, 1.2 Hz, 1H, 6-H), 7.19 (dd, J = 8.3, 1.2 Hz, 1H, 4-H), 7.05 (d, J = 8.8 Hz, 1H, 6'-H), 6.56 – 6.52 (m, 2H, 3'-h and 5'-H), 3.77 (s, 3H, 2'-OCH_3), 3.74 (s, 3H, 3-OCH), 1.03 (s, 9H, $OSi(CH_3)_2C(C\underline{H}_3)_3$), 0.28 (s, 6H, $OSi(C\underline{H}_3)_2C(CH_3)_3$).

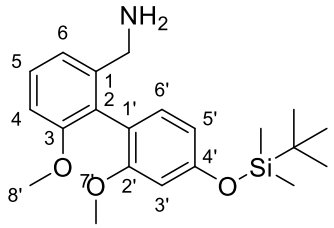
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 158.4 (C-4'), 158.0 (C-3), 157.9 (C-2'), 132.1 (C-6'), 131.9 (C-2), 129.2 (C-5), 124.8 (C-6), 118.6 (CN), 116.8 (C-1'), 115.7 (C-4), 115.6 (C-1), 111.8

(C-5'), 104.3 (C-3'), 56.4 (2'-OCH_3), 55.9 ((3-OCH_3), 25.8 ($OSi(CH_3)_2C(\underline{C}H_3)_3$), 18.5 ($OSi(CH_3)_2\underline{C}(CH_3)_3$), -4.2 ($OSi(\underline{C}H_3)_2C(CH_3)_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2232, 1612, 1512, 1459, 1448, 1309, 1265, 1206, 1166, 1067, 987, 937, 779.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{20}H_{25}NO_2Si^{\bullet+}$: 369.1760; found 369.1757.

3-Methoxy-2-(2-methoxy-4-((*tert*-butyldimethylsilyl)oxy)phenyl)benzylamine (213)



$C_{21}H_{31}NO_3Si$

M = 373.5680 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **212** (702 mg, 1.90 mmol), LAH (108 mg, 2.85 mmol) and $AlCl_3$ (355 mg, 2.66 mmol). Purification by FCC afforded the product **213** as an amber resin (639 mg, 1.71 mmol, 90%).

R_f: 0.26 (hexanes/EtOAc 2:1 + 1% NEt_3).

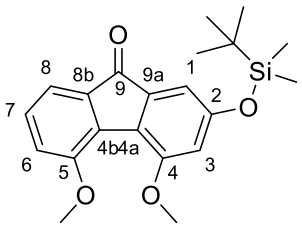
^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ (ppm) = 7.27 (t, *J* = 8.0 Hz, 1H, 5-H), 7.14 (ddt, *J* = 7.8, 1.3, 0.8 Hz, 1H, 6-H), 6.93 – 6.89 (m, 1H, 4-H), 6.90 (d, *J* = 8.1 Hz, 1H, 6'-H), 6.59 (d, *J* = 2.3 Hz, 1H, 3'-H), 6.53 (dd, *J* = 8.1, 2.3 Hz, 1H, 5'-H), 4.09 (d, *J* = 6.4 Hz, 2H, NH_2), 3.69 (s, 3H, 2'-OCH_3), 3.68 (s, 3H, 3-OCH_3), 1.05 (s, 9H, ($OSi(CH_3)_2C(C\underline{H}_3)_3$)), 0.30 (s, 6H, ($OSi(C\underline{H}_3)_2C(CH_3)_3$)).

^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ (ppm) = 159.2 (C-2'), 158.4 (C-3), 157.1 (C-4'), 142.2 (C-1), 132.9 (C-6'), 128.7 (C-5), 127.5 (C-2), 121.3 (C-6), 120.1 (C-1'), 112.3 (C-5'), 109.9 (C-4), 104.6 (C-3'), 56.1 (3-OCH_3), 55.8 (2'-OCH_3), 53.7 (CH_2NH_2), 26.2 ($OSi(CH_3)_2C(\underline{C}H_3)_3$), 19.0 ($OSi(CH_3)_2\underline{C}(CH_3)_3$), -4.1 ($OSi(\underline{C}H_3)_2C(CH_3)_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2931, 1578, 1509, 1464, 1293, 1253, 1200, 1162, 1036, 976, 837, 778.

HRMS (ESI): *m/z* = $[M+H]^+$ calcd for $C_{21}H_{32}NO_3Si^+$: 374.2146; found 374.2149.

2((*tert*-Butyldimethylsilyl)oxy)-4,5-dimethoxy-9*H*-fluoren-9-one (214)



$C_{21}H_{26}O_4Si$

M = 370.5200 g/mol

This compound was prepared in accordance with **General procedure A1** from amine **213** (598 mg, 1.60 mmol) and aqueous TBHP (70%, 0.620 mL, 6.40 mmol). Purification by FCC afforded the product **214** a red solid (25.0 mg, 0.0674 mmol, 4%).

R_f: 0.51 (hexanes/EtOAc 4:1).

M.p.: 59 – 60 °C.

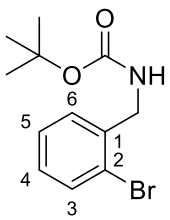
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.24 (dd, J = 6.8, 1.2 Hz, 1H, 8-H), 7.17 (dd, J = 8.2, 7.1 Hz, 1H, 7-H), 7.08 (dd, J = 8.1, 1.1 Hz, 1H, 6-H), 6.77 (d, J = 2.2 Hz, 1H, 1-H), 6.56 (d, J = 2.2 Hz, 1H, 3-H), 3.89 (s, 3H, 5-OCH_3), 3.88 (s, 3H, 4-OCH_3), 1.00 (s, 9H, $OSi(CH_3)_2C(C\underline{H}_3)_3$), 0.25 (d, J = 0.5 Hz, 6H, $OSi(C\underline{H}_3)_2C(CH_3)_3$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 194.1 (C-9), 158.5 (C-2), 156.2 (C-4), 154.8 (C-5), 137.5 (C-9a), 136.5 (C-8a), 132.3 (C-5a), 129.5 (C-7), 125.0 (C-4a), 121.8 (C-6), 117.5 (C-8), 112.3 (C-3), 109.3 (C-1), 57.6 (OCH_3), 57.2 (OCH_3), 25.9 ($OSi(CH_3)_2C(\underline{C}H_3)_3$), 18.7 ($OSi(CH_3)_2\underline{C}(CH_3)_3$), -4.1 ($OSi(\underline{C}H_3)_2C(CH_3)_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2952, 2930, 2857, 1710, 1600, 1471, 1444, 1360, 1316, 1272, 1258, 1193, 1148, 1061, 972, 909, 835, 779, 740.

HRMS (ESI): *m/z* = $[M+H]^+$ calcd for $C_{21}H_{27}O_4Si^+$: 371.1679; found 371.1672.

***N*-(*tert*-Butoxycarbonyl)-2-bromobenzylamine (217)**



$C_{12}H_{16}BrNO_2$

M = 286.1690 g/mol

To a solution of 2-bromophenylmethanamine (**216**, 3.00 g, 16.1 mmol, 1.00 equiv.) in DCM (50 mL) were added di-*tert*-butyl dicarbonate (4.57 g, 21.0 mmol, 1.30 equiv.) and trimethylamine (6.74 mL, 48.4 mmol, 3.00 equiv.). The resulting mixture was stirred at room temperature overnight. Upon completion of the reaction, the reaction mixture was washed with H_2O (3 x 20 mL), brine (3 x 20 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo*. Purification by FCC afforded the product **217** as a clear oil (4.08 g, 14.3 mmol, 89%).

R_f: 0.37 (hexanes/EtOAc 10:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.55 (dd, *J* = 7.6, 1.2 Hz, 1H, 3-H), 7.37 (dd, *J* = 7.7, 1.9 Hz, 1H, 6-H), 7.31 (td, *J* = 7.7, 1.2 Hz, 1H, 5-H), 7.16 (td, *J* = 7.7, 1.9 Hz, 1H, 4-H), 5.09 (s, 1H, $CH_2N\underline{H}$), 4.35 (d, *J* = 6.3 Hz, 2H, $C\underline{H}_2NH$), 1.43 (9H, s, $C(C\underline{H}_3)_3$).

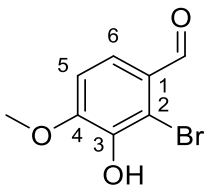
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 156.0 (NHCOO), 138.7 (C-1), 133.1 (C-3), 129.8 (C-6), 129.3 (C-4), 128.0 (C-5), 123.7 (C-2), 79.7 ($\underline{C}(CH_3)_3$), 45.2 ($\underline{C}H_2NH$), 28.5 ($C(\underline{C}H_3)_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3347, 2977, 2929, 2360, 2339, 1658, 1522, 1440, 1363, 1281, 1248, 1159, 1107, 1051, 1025, 950, 873, 752.

HRMS (EI): *m/z* = $[M-(CH_3)_3C]^{\bullet+}$ calcd for $C_8H_7{}^{79}BrNO_2{}^{\bullet+}$: 227.9660; found 227.9650.

Literature known compound.[271]

2-Bromo-3-hydroxy-4-methoxybenzaldehyde (225)



$C_8H_7BrO_3$

M = 231.0450 g/mol

This compound was prepared in accordance with **General procedure N** from 3-Hydroxy-4-methoxybenzaldehyde (**137**, 25.1 g, 165 mmol) and NBS (29.7 g, 165 mmol), using DCM (0.50 L) as the solvent. The product **225** was furnished as a white solid (36.3 g, 157 mmol, 95%) and used without further purification.

R_f: 0.18 (hexanes/EtOAc 4:1).

M.p.: 209 – 210 °C.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 10.11 (s, 1H, CHO), 7.41 (d, J = 8.5 Hz, 1H, 6-H), 7.14 (d, J = 8.5 Hz, 1H, 5-H), 3.92 (s, 3H, OCH_3).

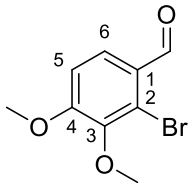
^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 191.0 (CO), 153.5 (C-4), 144.1 (C-3), 126.7 (C-1), 122.2 (C-6), 113.4 (C-2), 110.5 (C-5), 56.6 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3198, 1666, 1591, 1561, 1493, 1275, 1231, 1199, 1132, 1014, 804.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_8H_7{}^{79}BrO_3{}^{\bullet+}$: 229.9579; found 229.9569.

Literature known compound.[178]

2-Bromo-3,4-dimethoxybenzaldehyde (226)



$C_9H_9BrO_3$

M = 245.0720 g/mol

This compound was prepared in accordance with **General procedure O** from alcohol **225** (32.1 g, 139 mmol), K_2CO_3 (27.8 g, 278 mmol) and MeI (11.1 mL, 181 mmol). Purification by FCC afforded the product **226** as a white solid (31.5 g, 129 mmol, 93%).

R_f: 0.44 (hexanes/EtOAc 4:1).

M.p.: 84 – 85 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.26 (d, J = 0.8 Hz, 1H, CHO), 7.74 (d, J = 8.7 Hz, 1H, 6-H), 6.96 (dd, J = 8.7, 0.8 Hz, 1H, 5-H), 3.96 (s, 3H, 4-OCH_3), 3.88 (s, 3H, 3-OCH_3).

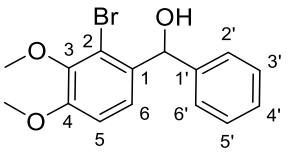
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.1 (CHO), 158.8 (C-4), 146.5 (C-3), 127.5 (C-1), 126.6 (C-6), 123.3 (C-2), 111.1 (C-5), 60.8 (4-OCH_3), 56.5 (3-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2942, 2861, 1677, 1579, 1488, 1446, 1256, 1216, 1140, 1020, 928, 808.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_9H_9{}^{79}BrO_3{}^{\bullet+}$: 243.9735; found 243.9731.

Literature known compound.[272]

(2-Bromo-3,4-dimethoxyphenyl)(phenyl)methanol (227)



$C_{15}H_{15}BrO_3$

M = 323.1860 g/mol

Bromobenzene (8.47 mL, 80.4 mmol, 1.20 equiv.) dissolved in dry diethylether (20 mL) was added slowly to an oven dried Schlenk flask charged equipped with a dripping funnel, a reflux condenser and charged with Mg (1.74 g, 73.7 mmol, 1.10 equiv.) in dry diethylether (0.20 L) under nitrogen atmosphere. After the magnesia had reacted completely, aldehyde **226** (16.4 g, 67.0 mmol, 1.00 equiv.) dissolved in dry diethylether (40 mL) was added slowly *via* dripping funnel. The reaction was stirred for 2 h before the reaction flask was placed in an ice-bath and water (20 mL) was added slowly. The organic phase was washed with brine (3 x 20 mL) and the solvent was removed *in vacuo*. Purification by FCC gave the product **227** as a white solid (13.6 g, 42.0 mmol, 63%).

R_f: 0.20 (hexanes/EtOAc 8:1).

M.p.: 103 – 104 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.43 – 7.38 (m, 2H, 2'-H and 6'-H), 7.34 (ddd, J = 8.0, 6.9, 0.9 Hz, 2H, 3'-H and 5'-H), 7.32 – 7.23 (m, 1H, 4'-H), 7.21 (d, J = 8.7 Hz, 1H, 6-H), 6.88 (d, J = 8.7 Hz, 1H, 5-H), 6.18 (d, J = 3.9 Hz, 1H, C<u>H</u>OH), 3.87 (s, 3H, 4-OCH_3), 3.85 (s, 3H, 3-OCH_3).

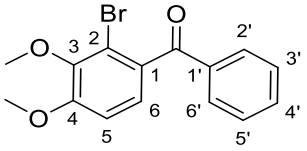
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 153.1 (C-4), 146.4 (C-3), 142.6 (C-1'), 135.8 (C-1), 128.6 (C-3' and C-5'), 127.8 (C-4'), 127.0 (C-2' and C-6'), 123.8 (C-6), 119.0 (C-2), 111.5 (C-5), 74.7 (CHOH), 60.6 (3-OCH_3), 56.2 (4-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3498, 1592, 1484, 1448, 1401, 1278, 1258, 1182, 1141, 1030, 1005, 921, 812, 726, 696, 661.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{15}{}^{79}BrO_3{}^{\bullet+}$: 322.0205; found 322.0197.

Literature known compound.[177] The synthesis was performed as described by Silveira and coworkers.[177]

(2-Bromo-3,4-dimethoxyphenyl)(phenyl)methanone (228)



$C_{15}H_{13}BrO_3$

M = 321.1700 g/mol

MnO_2 (73.0 g, 840 mmol, 20.0 equiv.) was added to a solution of alcohol **227** (13.6 g, 42.0 mmol, 1.00 equiv.) in DCM (0.20 L) and the mixture was stirred for 16 h at room temperature. The mixture was then filtered through a bed of celite, and the filtrate was concentrated *in vacuo*. Purification by FCC gave the product **228** as a white solid (11.7 g, 36.5 mmol, 87%).

R_f: 0.22 (hexanes/EtOAc 8:1).

M.p.: 117 – 118 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.81 (dt, *J* = 7.7, 1.1 Hz, 2H, 2'-H and 6'-H), 7.61 – 7.56 (m, 1H, 4'-H), 7.51 – 7.40 (m, 2H, 3'-H and 5'-H), 7.11 (d, *J* = 8.4 Hz, 1H, 6-H), 6.94 (d, *J* = 8.4 Hz, 1H. 5-H), 3.94 (s, 3H, 4-OCH_3), 3.90 (s, 3H, 3-OCH_3).

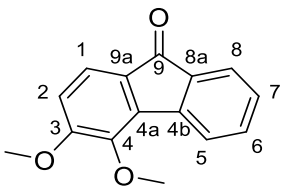
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 195.5 (CO), 155.1 (C-4), 146.9 (C-3), 136.9 (C-1'), 133.9 (C-1), 133.6 (C-4'), 130.4 (C-2' and C-6'), 128.7 (C-3' and C-5'), 125.3 (C-6), 116.3 (C-2), 111.1 (C-5), 60.8 (3-OCH_3), 56.4 (4-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2935, 1656, 1588, 1586, 1448, 1392, 1294, 1266, 1033, 964, 813, 719, 698.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{13}{}^{79}BrO_3{}^{\bullet+}$: 320.0048; found 320.0049.

Literature known compound.[177] The synthesis was performed as described by Silveira and coworkers.[177]

3,4-Dimethoxy-9*H*-fluoren-9-one (229)



$C_{15}H_{12}O_3$

M = 240.2580 g/mol

An oven dried Schlenk flask was charged with K_2CO_3 (8.13 g, 49.2 mmol, 2.05 equiv.), KOAc (4.83 g, 49.2 mmol, 2.05 equiv.), $Pd(PPh_3)_4$ (1.66 g, 1.44 mmol, 0.0600 equiv., 6 mol%), DavePhos (974 mg, 2.40 mmol, 0.100 equiv.) and DMA (50 mL) under nitrogen atmosphere and the resulting mixture was stirred for 15 min at room temperature, after which a solution of benzophenone **228** (7.71 g, 24.0 mmol, 1.00 equiv.) in DMA (15 mL) was added. The mixture was stirred for 22 h at 110 °C after which water (0.100 L) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with water (3 x 50 mL) and brine (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent removed *in vacuo*. Purification by FCC afforded the product **229** as a yellow solid (3.92 g, 16.3 mmol, 68%).

R_f: 0.32 (hexanes/EtOAc 8:1).

M.p.: 137 – 138 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.50 (dt, J = 7.3, 1.0 Hz, 1H, 8-H), 7.45 – 7.38 (m, 2H, 5-H and 6-H), 7.21 (td, J = 7.1, 1.5 Hz, 1H, 7-H), 7.16 (s, 1H, 1-H), 7.04 (s, 1H, 2-H), 3.97 (s, 3H, 3-OCH_3), 3.88 (s, 3H, 4-OCH_3).

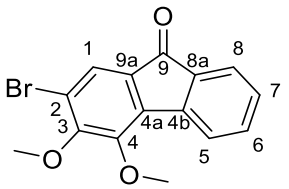
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 193.2 (C-9), 155.3 (C-3), 150.4 (C-4), 144.4 (C-4b), 139.8 (C-4a), 135.2 (C-8a), 134.6 (C-5), 128.5 (C-7), 127.1 (C-9a), 123.8 (C-8), 119.6 (C-6), 107.5 (C-1), 104.1 (C-2), 56.7 (3-OCH_3), 56.5 (4-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2923, 1703, 1588, 1499, 1458, 1264, 1243, 1209, 1114, 1080, 1024, 1010, 858, 764, 736, 714.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{12}O_3^{\bullet+}$ 240.0786; found 240.0782.

Literature known compound.[177] The synthesis was performed as described by Silveira and coworkers.[177]

2-Bromo-3,4-dimethoxy-9*H*-fluoren-9-one (231)



$C_{15}H_{11}BrO_3$

M = 319.1540 g/mol

Bromine (0.100 mL, 1.98 mmol, 1.10 eqiv.) was added to a solution of azafluorenone **229** (432 mg, 1.80 mmol, 1.00 equiv.) in acetic acid (20 mL) at 50 °C. After 4 h the reaction mixture

was carefully added to aqueous ammonia in an ice bath. The precipitate that formed was filtered off. Purification by FCC afforded the product **231** as a yellow solid (51.2 mg, 0.160 mmol, 9%).

R_f: 0.48 (hexanes/EtOAc 8:1).

M.p.: 135 – 136 °C.

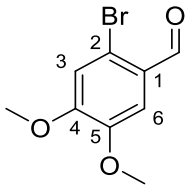
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.80 (dt, *J* = 7.5, 0.9 Hz, 1H, 5-H), 7.64 (ddd, *J* = 7.4, 1.3, 0.7 Hz, 1H, 8-H), 7.62 (s, 1H, 1-H), 7.50 (td, *J* = 7.5, 1.2 Hz, 1H, 6-H), 7.30 (td, *J* = 7.5, 1.0 Hz, 1H, 7-H), 4.02 (s, 3H, 4-OCH_3), 3.98 (s, 3H, 3-OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.7 (C-9), 156.4 (C-3), 149.7 (C-4), 142.5 (C-4b), 136.6 (C-4a), 135.2 (C-6), 134.2 (C-8a), 131.4 (C-9a), 129.2 (C-7), 124.8 (C-1), 124.5 (C-8), 124.0 (C-5), 118.3 (C-2), 61.0 (3-OCH_3), 60.8 (4-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2950, 1711, 1606, 1583, 1469, 1399, 1293, 1259, 1185, 1170, 1099, 1052, 993, 962, 874, 750, 718.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{11}{}^{79}BrO_3{}^{\bullet+}$ 317.9892; found 317.9881.

2-Bromo-4,5-dimethoxybenzaldehyde (234)



$C_9H_9BrO_3$

M = 245.0720 g/mol

To a solution of 3,4-dimethoxybenzaldehyde (**233**, 997 mg, 6.00 mmol, 1.00 equiv.) in methanol (20 mL) bromine (0.338 mL, 6.60 mmol, 1.10 equiv.) was added dropwise at 0 °C. After addition the mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was diluted with H_2O (20 mL) and the pH adjusted to pH = 10. The precipitated crystals were collected by filtration, washed with H_2O (3 x 20 mL), and then dried *in vacuo* to afford the product **234** as a white solid (1.26 g, 5.13 mmol, 86%).

R_f: 0.30 (hexanes/EtOAc 8:1).

M.p.: 149 – 150 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 10.16 (s, 1H, CHO), 7.39 (s, 1H, 6-H), 7.08 (s, 1H, 3-H), 3.92 (s, 3H, 4-OCH_3), 3.88 (s, 3H, 5-OCH_3).

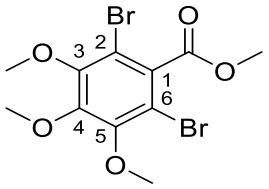
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 191.0 (CO), 155.3 (C-4), 149.7 (C-5), 127.0 (C-1), 120.7 (C-2), 116.1 (C-3), 111.0 (C-6), 57.0 (4-OCH_3), 56.6 (5-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1668, 1586, 1505, 1446, 1385, 1269, 1218, 1154, 1041, 1015, 979, 866, 812, 737, 655.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_9H_9{}^{79}BrO_3{}^{\bullet+}$: 243.9735; found 243.9740.

Literature known compound.[273]

Methyl 2,6-dibromo-3,4,5-trimethoxybenzoate (238)



$C_{11}H_{12}Br_2O_5$

M = 384.0200 g/mol

This compound was prepared in accordance with **General procedure N** from methyl 3,4,5-trimethoxybenzoate (**237**, 10.0 g, 43.4 mmol) and NBS (16.1 g, 90.0 mmol), using MeCN (0.30 L) as the solvent to afford the product **238** as a white solid (16.5 g, 42.9 mmol, 99%).

R_f: 0.18 (hexanes/EtOAc 8:1).

M.p.: 73 – 75 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.97 (s, 3H, $COOCH_3$), 3.94 (s, 3H, 4-OCH_3), 3.89 (s, 6H, 3-OCH_3 and 5-OCH_3).

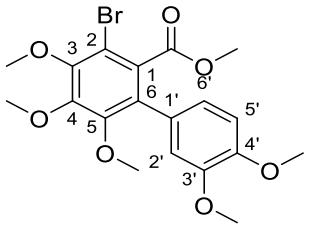
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 166.4 (COO), 151.3 (C-3 and C-5), 148.8 (C-4), 133.6 (C-1), 110.0 (C-2), 61.6 (4-OCH_3), 61.3 (3-OCH_3 and 5-OCH_3), 53.3 (COO<u>C</u>H_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2942, 1737, 1445, 1380, 1339, 1220, 1084, 1025, 1003, 970, 906, 788, 724.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{11}H_{12}{}^{79}Br_2O_5{}^{\bullet+}$: 381.9051; found 381.9041.

Literature known compound.[274]

Methyl 3-bromo-3',4,4',5,6-pentamethoxy-[1,1'-biphenyl]-2-carboxylate (239)



$C_{19}H_{21}BrO_7$

M = 441.2740 g/mol

This compound was prepared in accordance with **General procedure G** from benzoat **238** (2.73 g, 7.10 mmol), boronic acid **191s** (1.29 g, 7.10 mmol), $Pd(PPh_3)_4$ (410 mg, 0.355 mmol) and Cs_2CO_3 (4.63 g, 14.2 mmol). Purification by FCC afforded the product **239** as a yellow oil (803 mg, 3.49 mmol, 49%).

R_f: 0.10 (hexanes/EtOAc 8:1).

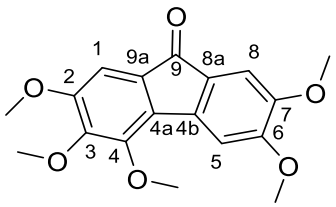
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.89 – 6.85 (m, 3H, 2'-H and 5'-H and 6'-H), 3.96 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.61 (s, 3H, $COOCH_3$), 3.59 (s, 3H, OCH_3).

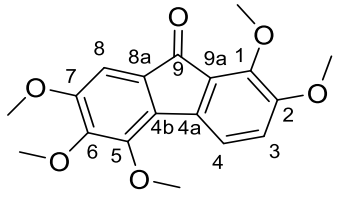
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 167.65 (COO), 151.43 ($\underline{C}OCH_3$), 150.71 ($\underline{C}OCH_3$), 148.77 ($\underline{C}OCH_3$), 148.49 ($\underline{C}OCH_3$), 148.44 ($\underline{C}OCH_3$), 132.46 (C-1 or C-6 or C-1'), 130.95 (C-1 or C-6 or C-1'), 127.23 (C-1 or C-6 or C-1'), 122.05 (C-2' or C-5' or C-6'), 112.97 (C-2' or C-5' or C-6'), 110.77 (C-2' or C-5' or C-6'), 109.34 (C-2), 61.43 (OCH_3), 61.29 (OCH_3), 56.00 (OCH_3), 55.92 (OCH_3), 52.63 ($COO\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2964, 1728, 1514, 1442, 1384, 1336, 1252, 1218, 1145, 1076, 1022, 1005, 971, 869, 917, 736, 721.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{19}H_{21}{}^{79}BrO_7{}^{\bullet+}$: 440.0471; found 440.0461.

2,3,4,6,7-Pentamethoxy-9*H*-fluoren-9-one (241) and **1,2,5,6,7-pentamethoxy-9*H*-fluoren-9-one (242)**





$C_{18}H_{18}O_6$

M = 330.3360 g/mol

These compounds were prepared over three steps. Reaction of ester **239** (185 mg, 0.420 mmol) with KOH (94.3 mg, 1.68 mmol) in accordance with **General procedure D** gave the crude carboxylic acid **240** (126 mg), which was used directly without further purification. Reaction of crude carboxylic acid **240** (126 mg) with PPA (1.26 g) in accordance with **General procedure C** gave a crude mixture of monodemethylated fluorenones (90.4 mg), which was used directly without further purification. The crude fluorenone mixture was reacted with MeI (0.0523 mL, 0.840 mmol) and K_2CO_3 (84.1 mg, 0.840 mmol) in accordance with with **General procedure O**. Purification by FCC afforded the fluorenone **241** as a yellow solid (61.3 mg, 0.186 mmol, 44%). The compound **241** was accompanied by its regioisomer **242**, obtained as a yellow solid (17.1 mg, 0.0518 mmol, 12%).

2,3,4,6,7-Pentamethoxy-9*H*-fluoren-9-one **241**:

R_f: 0.46 (hexanes/EtOAc 2:1).

M.p.: 147 – 149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.24 (s, 1H, 5-H), 7.14 (s, 1H, 8-H), 7.00 (s, 1H, 1-H), 4.01 (bs, 3H, OCH_3), 3.99 (s, 3H, 6-OCH_3), 3.94 (s, 3H, 3-OCH_3), 3.90 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 192.5 (C-9), 154.5 (C-6), 154.0 ($\underline{C}OCH_3$), 148.7 (C-7), 147.7 (C-3), 138.7 (C-4b), 130.6 (C-5), 129.1 (C-4), 126.9 (C-8a), 107.5 (C-8), 106.4 (C-5), 104.6 (C-1), 61.2 (3-OCH_3), 60.9 (OCH_3), 56.6 (OCH_3), 56.4 (OCH_3), 56.4 (8-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1703, 1588, 1480,1434, 1462, 1420, 1405, 1300, 1244, 1104, 1066, 996, 874, 767.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{18}H_{18}O_6^{\bullet+}$: 330.1103; found 330.1094.

Literature known compound.[275]

1,2,5,6,7-Pentamethoxy-9*H*-fluoren-9-one **242**:

R_f: 0.50 (hexanes/EtOAc 2:1).

M.p.: 124 – 125°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.34 (d, *J* = 8.0 Hz, 1H, 4-H), 7.02 (s, 1H, 8-H), 6.86 (d, *J* = 8.0 Hz, 1H, 3-H), 4.07 (s, 3H, 5-OCH_3 or 7-OCH_3), 3.98 (s, 3H, 1-OCH_3), 3.95 (s, 3H, 6-OCH_3), 3.90 (s, 3H, 5-OCH_3 or 7-OCH_3), 3.87 (s, 3H, 2-OCH_3)

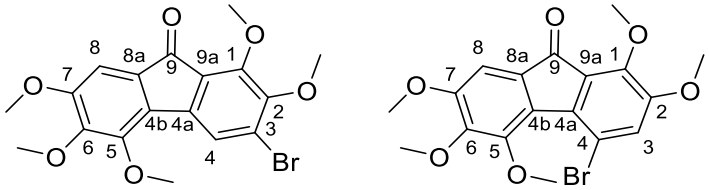
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 190.8 (C-9), 154.0 (C-5 or C-7), 153.3 (C-2), 149.3 (C-5 or C-7), 148.9 (C-1), 148.1 (C-6), 136.0 (C-4a), 130.5 (C-8a), 129.7 (C-4b), 125.3 (C-9a), 118.2 (C-4), 117.0 (C-3), 104.1 (C-8), 62.2 (5-OCH_3 or 7-OCH_3), 61.2 (6-OCH_3), 60.7 (1-OCH_3), 56.6 (2-OCH_3 or 5-OCH_3 or 7-OCH_3), 56.6 (2-OCH_3 or 5-OCH_3 or 7-OCH_3)

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2927, 1698, 1597, 1465, 1428, 1289, 1268, 1254, 1189, 1134, 1108, 1049, 993, 801.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{18}H_{18}O_6^{\bullet+}$: 330.1103; found 330.1094.

Literature known compound.[67]

3-Bromo-1,2,5,6,7-pentamethoxy-9*H*-fluoren-9-one or 4-bromo-1,2,5,6,7-pentamethoxy-9*H*-fluoren-9-one (244)



$C_{18}H_{17}BrO_6$

M = 409.2320 g/mol

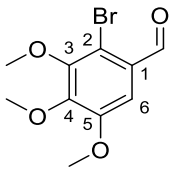
This compound was prepared in accordance with **General procedure N** from fluorenone **242** (19.8 mg, 0.0600 mmol) and NBS (11.9 g, 0.0660 mmol), using MeCN (10 mL) as the solvent to afford the crude product **244** as a yellow solid (2.00 mg, 0.00489 mmol, 8%).

R_f: 0.11 (hexanes/EtOAc 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.1 (1H, s), 7.1 (1H, s), 4.0 (3H, s), 3.9 (3H, s), 3.9 (3H, s), 3.9 (3H, s), 3.9 (3H, s).

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{18}H_{17}BrO_6^{\bullet+}$: 408.0209; found 408.0211.

2-Bromo-3,4,5-trimethoxybenzaldehyde (247)



$C_{10}H_{11}BrO_4$

M = 275.0980 g/mol

This compound was prepared in accordance with **General procedure N** from aldehyde **245** (7.59 g, 38.7 mmol) and NBS (7.58 g, 42.6 mmol), using MeCN (0.20 L) as the solvent to afford the product as a white solid (8.45 g, 30.8 mmol, 80%).

R_f: 0.41 (hexanes/EtOAc 8:1).

M.p.: 70 – 71 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.30 (s, 1H, CHO), 7.31 (s, 1H, 6-H), 3.98 (s, 3H, 4-OCH_3), 3.91 (s, 3H, 3-OCH_3 or 5-OCH_3), 3.91 (s, 3H3-OCH_3 or 5-OCH_3).

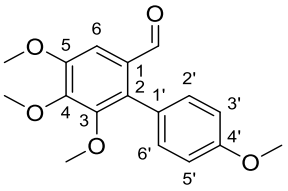
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.1 (CHO), 153.1 (C-3 or C-5), 150.8 (C-3 or C-5), 148.7 (C-4), 128.8 (C-1), 115.7 (C-2), 107.5 (C-6), 61.3 (4-OCH_3), 61.2 (3-OCH_3 or 5-OCH_3), 56.3 (3-OCH_3 or 5-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1683, 1449, 1383, 1325, 1197, 1164, 1104, 1001, 980, 920, 859, 774, 725.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{10}H_{11}{}^{79}BrO_4{}^{\bullet+}$: 273.9841; found 273.9836.

Literature known compound.[276]

4,4',5,6-Tetramethoxy-[1,1'-biphenyl]-2-carbaldehyde (248)



$C_{17}H_{18}O_5$

M = 302.3260 g/mol

This compound was prepared in accordance with **General procedure G** from aldehyde **247** (6.88 mg, 2.50 mmol), boronic acid **191c** (494 mg, 3.25 mmol), $Pd(PPh_3)_4$ (144 mg, 0.125 mmol) and K_2CO_3 (501 mg, 5.00 mmol). Purification by FCC afforded the product **248** as a yellow oil (640 mg, 2.12 mmol, 85%).

R_f: 0.37 (hexanes/EtOAc 4:1).

M.p.: 69 – 70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.68 (s, 1H, CHO), 7.35 (s, 1H, 6-H), 7.28 – 7.23 (m, 2H, 2'-H and 6'-H), 6.98 (d, J = 8.6 Hz, 2H, 3'-H and 5'-H), 4.00 (s, 3H, 4'-OCH_3), 3.95 (s, 3H, 3-OCH_3 or 5-OCH_3), 3.87 (s, 3H, 4-OCH_3), 3.59 (s, 3H, 3-OCH_3 or 5-OCH_3).

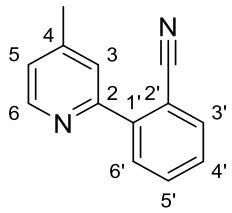
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.7 (CO), 159.5 (C-4'), 153.1 (C-3 or C-5), 151.4 (C-3 or C-5), 147.8 (C-4), 134.4 (C-2), 132.4 (C-2' and C-6'), 130.0 (C-1), 124.9 (C-1'), 113.6 (C-3' and C-5'), 105.4 (C-6), 61.2 (3-OCH_3, 4-OCH_3 or 5-OCH_3), 61.2 (3-OCH_3, 4-OCH_3 or 5-OCH_3), 56.3 (3-OCH_3, 4-OCH_3 or 5-OCH_3), 55.5 (4-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2938, 2836, 1682, 1586, 1480, 1327, 1244, 1141, 1091, 1032, 999, 832, 733.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{17}H_{18}O_5^{\bullet+}$: 302.1154; found 302.1150.

Literature known compound.[277]

2-(4-Methylpyridin-2-yl)benzonitrile (252)



$C_{13}H_{10}N_2$

M = 194.2370 g/mol

This compound was prepared in accordance with **General procedure P** from 2-phenylpyridine **260** (846 mg, 5.00 mmol), AIBN (4.11 g, 25.0 mmol), and $Cu(OAc)_2$ (999 mg, 5.50 mmol). Purification by FCC afforded the product **252** as a white solid (452 mg, 2.33 mmol, 47%).

R_f: 0.35 (hexanes/EtOAc 2:1).

M.p.: 55 – 56 °C.

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 8.59 (dd, J = 5.0, 0.9 Hz, 1H, 6-H), 7.82 – 7.78 (m, 2H, 3'-C and 6'-C), 7.72 – 7.67 (m, 1H, 5'-C), 7.58 – 7.56 (m, 1H, 3-C), 7.51 (td, J = 7.6, 1.4 Hz, 1H, 4'-C), 7.20 (ddd, J = 5.0, 1.6, 0.8 Hz, 1H, 5-C), 2.45 (s, 3H, CH_3).

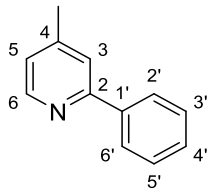
^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 155.9 (C-2), 150.0 (C-6), 148.7 (C-4), 144.2 (C-1'), 134.7 (C-3' or C-6'), 133.2 (C-5'), 130.4 (C-3' or C-6'), 129.1 (C-4'), 124.8 (C-5), 124.5 (C-3), 119.2 (CN), 111.7 (C-2'), 21.5 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2923, 2223, 1713, 1703, 1606, 1596, 1466, 1278, 1189, 832, 768, 750.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{13}H_{10}N_2^{\bullet+}$: 194.0844; found 194.0846.

Literature known compound.[188]

4-Methyl-2-phenylpyridine (260)



$C_{12}H_{11}N$

M = 169.2270 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromo-4-picoline (**250**, 3.78 g, 21.3 mmol), phenylboronic acid **191** (3.90 g, 32.0 mmol), $Pd(PPh_3)_4$ (1.23 g, 1.07 mmol) and K_2CO_3 (7.04 g, 42.6 mmol). Purification by FCC afforded the product **260** as an off-white solid (2.40 g, 14.2 mmol, 67%).

R_f: 0.47 (hexanes/EtOAc 8:1).

M.p.: 50 – 51 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.55 (d, *J* = 5.0 Hz, 1H, 6-H), 8.01 – 7.94 (m, 2H, 2'-H and 6'-H), 7.57 – 7.53 (m, 1H, 3-H), 7.51 – 7.44 (m, 2H, 3'-H and 5'-H), 7.43 – 7.37 (m, 1H, 4'-H), 7.06 (dt, *J* = 5.0, 1.1 Hz, 1H, 5-H), 2.42 (s, 3H, CH_3).

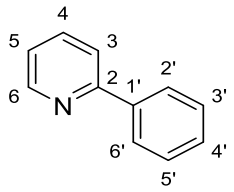
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 157.5 (C-2), 149.6 (C-6), 147.9 (C-4), 139.7 (C-1'), 128.9 (C-4'), 128.8 (C-2' and C-6'), 127.1 (C-3' and C-5'), 123.3 (C-5), 121.7 (C-3), 21.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1598, 1558, 1470, 1445, 896, 868, 828, 776, 741, 689.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{12}H_{11}N^{\bullet+}$: 169.0891; found 169.0889.

Literature known compound.[278]

2-phenylpyridine (261)



$C_{11}H_9N$

M = 155.2000 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromopyridine (**263**, 1.53 g, 9.70 mmol), phenylboronic acid (**191**, 1.77 g, 14.5 mmol), $Pd(OAc)_2$ (110 mg, 0.485 mmol), SPhos (796 mg, 1.94 mmol) and K_2CO_3 (3.21 g, 19.4 mmol). Purification by FCC afforded the product **261** as a yellow oil (775 mg, 4.99 mmol, 51%).

R_f: 0.40 (hexanes/EtOAc 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.73 – 8.68 (m, 1H, 6-H), 8.02 – 7.96 (m, 2H, 3'-H and C-5'), 7.80 – 7.70 (m, 2H, 3-H and 4-H), 7.52 – 7.45 (m, 2H, 2'-H and C-6'), 7.45 – 7.39 (m, 1H, 4'-H), 7.23 (ddd, J = 6.4, 4.8, 2.2 Hz, 1H, 5-H).

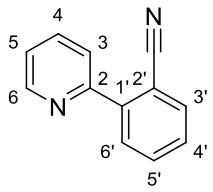
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 157.6 (C-2), 149.8 (C-6), 139.5 (C-1'), 136.9 (C-4), 129.1 (C-4'), 128.9 (C-2' and C-6'), 127.1 (C-3' and C-5', 122.2 (C-5), 120.7 (C-3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3062, 1580, 1564, 1468, 1449, 1424, 1152, 1074, 1020, 988, 738, 692.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{11}H_9N^{\bullet+}$: 155.0735; found 155.0726.

Literature known compound.[279]

2-(Pyridin-2-yl)benzonitrile (262)



$C_{12}H_8N_2$

M = 180.2100 g/mol

This compound was prepared in accordance with **General procedure P** from 2-phenylpyridine (**261**, 435 mg, 2.80 mmol), AIBN (1.77 g, 10.8 mmol), and $Cu(OAc)_2$ (559 mg, 3.08 mmol). Purification by FCC afforded the product **262** as light-yellow oil (258 mg, 1.41 mmol, 51%).

R_f: 0.28 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.78 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H, 6-H), 7.87 – 7.76 (m, 4H, 4-H and 3'-H and H_{arom}), 7.70 (td, J = 7.7, 1.4 H, 1H, 3-H), 7.51 (td, J = 7.7, 1.3 Hz, 1H, H_{arom}), 7.36 (ddd, J = 7.4, 4.8, 1.3 Hz, 1H, 5-H).

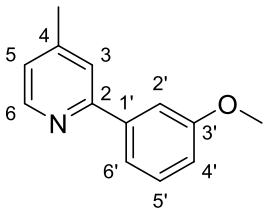
^{13}C NMR (101 MHz, $CDCl_3$): 155.4 (C-2), 150.1 (C-6), 143.6 (C-1'), 137.0 (C-4), 134.3 (C_{arom}), 133.0 (C-3), 130.1 (C_{arom}), 128.9 (C_{arom}), 123.5 (C-5), 123.4 (C_{arom}), 118.8 (CN), 111.2 (C-2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3358, 2225, 1716, 1587, 1560, 1465, 1432, 1302, 1274, 1191, 1152, 1063, 994, 792, 760.

HRMS (EI): m/z calcd for $C_{12}H_8N_2$ $[M]^{\bullet+}$ 180.0687; found 180.0680.

Literature known compound.[280]

2-(3-Methoxyphenyl)-4-methylpyridine (264)



$C_{13}H_{13}N_2$

M = 199.2530 g/mol

This compound was prepared in accordance with **General procedure G** from 2-bromo-4-picoline (**250**, 1.10 g, 6.20 mmol), 3-methoxyphenylboronic acid (**191k**, 1.13 g, 7.44 mmol), $Pd(PPh_3)_4$ (358 mg, 0.310 mmol) and K_2CO_3 (2.05 g, 12.4 mmol). Purification by FCC afforded the product **264** as a white solid (1.03 g, 5.17 mmol, 83%).

R_f: 0.37 (hexanes/EtOAc 2:1).

M.p.: 59 – 60 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.5 (dd, J = 5.0, 0.9 Hz, 1H, 6-H), 7.6 (dd, J = 2.7, 1.6 Hz, 1H, 2'-H), 7.5 – 7.5 (m, 2H, 3-H and 6'-H), 7.4 (t, J = 7.9 Hz, 1H, 5'-H), 7.1 (ddd, J = 5.1,

1.7, 0.9 Hz, 1H, 5-H), 7.0 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H, 4'-H), 3.9 (s, 3H, OCH_3), 2.4 (3H, s, CH_3).

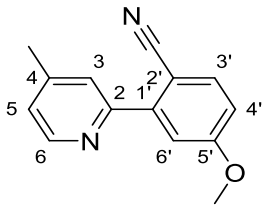
^{13}C NMR (101 MHz, $CDCl_3$): *δ* (ppm) = 160.2 (C-3'), 157.3 (C-2), 149.5 (C-6), 147.9 (C-4), 141.2 (C-1'), 129.8 (C-5'), 123.4 (C-5), 121.8 (C-3), 119.5 (C-6'), 115.2 (C-4'), 112.1 (C-2'), 55.5 (OCH_3), 21.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3002, 2955, 1587, 1599, 1491, 1457, 1429, 1300, 1232, 1173, 1036, 917, 874, 809, 789, 752, 691.

HRMS (EI): *m*/*z* = $[M-H]^{\bullet-}$ calcd for $C_{13}H_{12}N_2^{\bullet-}$: 198.0924; found 198.0919.

Literature known compound.[281]

4-Methoxy-2-(4-methylpyridin-2-yl)benzonitrile (265)



$C_{14}H_{12}N_2O$

M = 224.2630 g/mol

This compound was prepared in accordance with **General procedure P** from 2-phenylpyridine **264** (917 mg, 4.60 mmol), AIBN (3.78 g, 23.0 mmol), and $Cu(OAc)_2$ (919 mg, 5.06 mmol). Purification by FCC afforded the product **265** as brown-yellow solid (449 mg, 2.00 mmol, 44%).

R_f: 0.23 (hexanes/EtOAc 8:1).

M.p.: 115 – 116 °C.

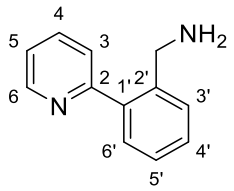
^{1}H NMR (400 MHz, CD_2Cl_2): *δ* (ppm) = 8.58 (dd, *J* = 5.0, 0.8 Hz, 1H, 6-H), 7.71 (d, *J* = 8.6 Hz, 1H, 3'-H), 7.59 – 7.57 (m, 1H, 3-H), 7.30 (d, *J* = 2.6 Hz, 1H, 6'-H), 7.20 (ddd, *J* = 5.0, 1.5, 0.7 Hz, 1H, 5-H), 7.01 (dd, *J* = 8.6, 2.6 Hz, 1H, 4'-H), 3.91 (s, 3H, OCH_3), 2.45 (s, 3H, CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): *δ* (ppm) = 162.8 (C-5'), 155.2 (C-2), 149.4 (C-6), 148.2 (C-4), 145.7 (C-1'), 135.8 (C-3'), 124.3 (C-5), 124.0 (C-3), 119.0 (CN), 115.2 (C-6'), 114.5 (C-4'), 102.8 (C-4'), 55.8 (OCH_3), 20.9 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2218, 1599, 1560, 1457, 1436, 1305, 1231, 1052, 1035, 875, 823, 692.

HRMS (EI): *m*/*z* = $[M-H]^{\bullet-}$ calcd for $C_{14}H_{11}N_2O^{\bullet-}$: 223.0877; found 223.0868.

(2-(pyridin-2-yl)phenyl)methanamine (266)



$C_{12}H_{12}N_2$

M = 184.2420 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **262** (847 mg, 4.70 mmol), LAH (223 mg, 5.88 mmol) and $AlCl_3$ (2.51 g, 18.8 mmol). Purification by FCC afforded the product **266** as a black oil (210 mg, 1.14 mmol, 24%).

R_f: 0.50 (DCM + 1% NEt_3).

^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ (ppm) = 8.70 – 8.65 (m, 1H, 6-H), 7.94 (td, *J* = 7.7, 1.8 Hz, 1H, H_{arom}), 7.65 (dt, *J* = 7.9, 1.1 Hz, 1H, H_{arom}), 7.58 (dd, *J* = 7.6, 1.5 Hz, 1H, H_{arom}), 7.48 (td, *J* = 6.7, 6.1, 1.7 Hz, 1H, H_{arom}), 7.46 – 7.39 (m, 3H, H_{arom}), 3.77 (s, 2H, H_{arom}).

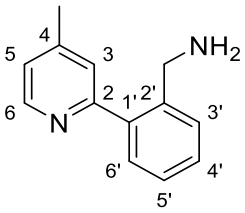
^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ (ppm) = 158.5 (C-2), 148.7 (C-6), 139.6 (C_{arom}), 138.3 (C_{arom}), 137.3 (C_{arom}), 130.1 (C_{arom}), 129.7 (C_{arom}), 128.6 (C_{arom}), 127.5 (C_{arom}), 124.0 (C_{arom}), 122.4 (C_{arom}).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3346, 2966, 1587, 1561, 1470, 1443, 1426, 1301, 1023, 798, 748.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{12}H_{12}N_2^{\bullet+}$: 184.1000; found 184.1003.

Literature known compound.[280]

(2-(4-Methylpyridin-2-yl)phenyl)methanamine (267)



$C_{13}H_{14}N_2$

M = 198.2690 g/mol

This compound was prepared in accordance with **General procedure H** from nitrile **252** (447 mg, 2.30 mmol), LAH (349 mg, 9.20 mmol) and $AlCl_3$ (1.23 g, 9.20 mmol). Purification by FCC afforded the product **267** as a black oil (160 mg, 0.807 mmol, 35%).

R_f: 0.20 (DCM + 1% NEt_3).

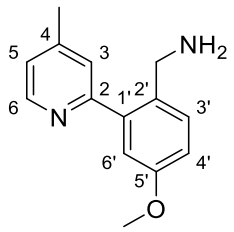
^{1}H NMR (400 MHz, MeOD): δ (ppm) = 8.48 (dd, J = 5.1, 0.8 Hz, 1H, 6-H), 7.53 (1H, dd, J = 7.8, 1.8 Hz, H_{arom}), 7.49 – 7.40 (4H, m, H_{arom}), 7.30 – 7.25 (1H, m, 5-H), 3.77 (s, 2H, CH_2), 2.46 (s, 3H, CH_3).

^{13}C NMR (101 MHz, MeOD): δ (ppm) = 160.3 (C-2), 150.8 (C-4), 149.2 (C-6), 141.4 (C-2'), 139.4 (C-1'), 131.2 (C_{arom}), 131.0 (C_{arom}), 130.2 (C_{arom}), 129.0 (C_{arom}), 126.4 (C_{arom}), 124.7 (C-5), 44.6 (CH_2), 21.1 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) =3356, 2922, 1602, 1558, 1473, 1445, 1396, 1297, 993, 866, 829, 775, 754.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{13}H_{14}N_2^{\bullet+}$: 198.1157; found 198.1148.

(4-Methoxy-2-(4-methylpyridin-2-yl)phenyl)methanamine (268)



$C_{14}H_{16}N_2O$

M = 228.2950 g/mol

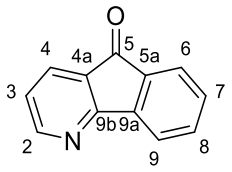
This compound was prepared in accordance with **General procedure H** from nitrile **265** (449 mg, 2.00 mmol), LAH (304 mg, 8.00 mmol) and $AlCl_3$ (1.07 g, 8.00 mmol). Attempts at purification by FCC afforded the crude product **268** as a black oil (166 mg, 0.727 mmol, 36%).

R_f: 0.15 (DCM + 1% NEt_3).

^{1}H NMR (400 MHz, MeOD): δ (ppm) = 8.5 (dd, J = 5.1, 0.8 Hz, 1H), 7.6 (dd, J = 1.6, 0.8 Hz, 1H), 7.5 (d, J = 8.5 Hz, 1H), 7.3 (ddd, J = 5.2, 1.6, 0.8 Hz, 1H), 7.1 (d, J = 2.7 Hz, 1H), 7.0 (dd, J = 8.4, 2.7 Hz, 1H), 3.9 (s, 3H), 3.3 (s, 2H), 2.5 (s, 3H).

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{14}H_{16}N_2O^{\bullet+}$: 180.1263; found 228.1258.

5*H*-Indeno[1,2-*b*]pyridin-5-one (269)



$C_{12}H_7NO$

M = 181.1940 g/mol

This compound was prepared in accordance with **General procedure A2** from pyridinemethanol **270** (50.0 mg, 0.270 mmol) and TBHP (5.5 M in decane, 0.196 mL, 1.08 mmol). Purification by FCC afforded the product **269** as an off-white solid (20.0 mg, 0.110 mmol, 41%).

R_f: 0.16 (hexanes/EtOAc 8:1).

M.p.: 137 – 138 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 8.60 (dd, *J* = 5.1, 1.6 Hz, 1H, 2-H), 7.87 (dd, *J* = 7.5, 1.6 Hz, 1H, 4-H), 7.84 (dt, *J* = 7.5, 1.0 Hz, 1H, 9-H), 7.70 (dt, *J* = 7.4, 1.0 Hz, 1H, 6-H), 7.62 (td, *J* = 7.5, 1.1 Hz, 1H, 8-H), 7.45 (td, *J* = 7.4, 1.0 Hz, 1H, 7-H), 7.22 (dd, *J* = 7.5, 5.1 Hz, 1H, 3-H).

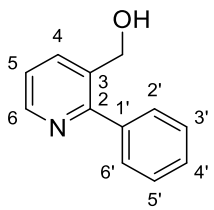
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 192.0 (C-5), 165.4 (C-9b), 154.5 (C-2), 144.1 (C-9a), 135.7 (C-8), 135.2 (C-5a), 131.5 (C-4), 131.3 (C-7), 128.7 (C-4a), 124.3 (C-6), 123.7 (C-3), 121.2 (C-9).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3052, 2921, 1713, 1591, 1404, 1289, 1170, 1092, 917, 741.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{12}H_7NO^{\bullet+}$: 181.0528; found 181.0522.

Literature known compound.[191]

(2-Phenylpyridin-3-yl)methanol (270)



$C_{12}H_{11}NO$

M = 185.2260 g/mol

This compound was prepared in accordance with **General procedure Q** from ester **273** (1.61 g, 7.10 mmol), LAH (539 mg, 14.2 mmol). Purification by FCC afforded the product **270** as an off-white solid (710 mg, 3.83 mmol, 54%).

R_f: 0.17 (hexanes/EtOAc 2:1).

M.p.: 99 – 100 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 8.56 (dd, *J* = 4.8, 1.7 Hz, 1H, 6-H), 7.91 (dd, *J* = 7.8, 1.7 Hz, 1H, 4-H), 7.53 – 7.49 (m, 2H, 2‘-H), 7.48 – 7.41 (m, 3H, 3‘-H and 4‘-H), 7.30 (1H, dd, *J* = 7.8, 4.8 Hz, 5-H), 4.63 (2H, s, CH_2).

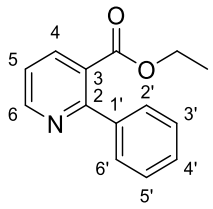
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 158.1 (C-2), 148.6 (C-6), 140.2 (C-1’), 136.7 (C-4), 134.4 (C-3), 129.4 (C-2’), 128.6 (C-4’), 128.5 (C-3’), 122.7 (C-5), 62.3 (CH_2).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3141, 2963, 1584, 1439, 1259, 1080, 1013, 788, 745, 700.

HRMS (EI): *m*/*z* = $[M-H]^{\bullet-}$ calcd for $C_{12}H_{10}NO^{\bullet-}$ 184.0768; found 184.0756.

Literature known compound.[191]

Ethyl 2-phenylnicotinate (273)



$C_{14}H_{13}NO_2$

M = 227.2630 g/mol

This compound was prepared in accordance with **General procedure G** from ethyl 2-chloronicotinate (**272**, 3.36 g, 18.1 mmol), phenylboronic acid (**191**, 3.31 g, 27.2 mmol), $Pd(OAc)_2$ (205 mg, 0.905 mmol), SPhos (1.49 g, 3.62 mmol) and K_2CO_3 (5.98 g, 36.2 mmol). Purification by FCC afforded the product **273** as a yellow oil (1.65 g, 7.24 mmol, 40%).

R_f: 0.23 (hexanes/EtOAc 8:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 8.75 (dd, *J* = 4.8, 1.8 Hz, 1H, 6-H), 8.08 (dd, *J* = 7.8, 1.8 Hz, 1H, 4-H), 7.55 – 7.51 (m, 2H, 2‘-H and 6’-H), 7.45 – 7.41 (m, 3H, 3‘-H, 4-H and 5’-H),

7.35 (dd, *J* = 7.8, 4.8 Hz, 1H, 5-H), 4.15 (q, *J* = 7.1 Hz, 2H, OC<u>H</u>$_2$CH$_3$), 1.08 (t, *J* = 7.1 Hz, 3H, OCH$_2$C<u>H</u>$_3$).

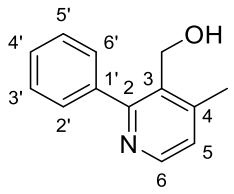
^{13}C NMR (101 MHz, CD_2Cl_2): *δ* (ppm) = 168.4 (COO), 158.9 (C-2), 151.5 (C-6), 140.8 (C-1'), 138.0 (C-4), 129.0 (C-2' and C-6'), 128.9 (C-4'), 128.4 (C-3' and C-5'), 127.8 (C-3), 122.0 (C-5), 61.8 (O<u>C</u>H$_2$CH$_3$), 13.9 (OCH$_2$<u>C</u>H$_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2980, 1712, 1559, 1427, 1279, 1208, 1128, 1095, 1053, 1018, 753, 696.

HRMS (EI): *m*/*z* = [M]$^{\bullet+}$ calcd for $C_{14}H_{13}NO_2^{\bullet+}$ 227.0946; found 227.0938.

Literature known compound.[282]

(4-Methyl-2-phenylpyridin-3-yl)methanol (274)



$C_{13}H_{13}NO$

M = 199.2530 g/mol

This compound was prepared in accordance with **General procedure Q** from ester **130** (603 mg, 2.50 mmol) and LAH (190 mg, 5.00 mmol). Purification by FCC afforded the product **274** as a white solid (325 mg, 1.63 mmol, 65%).

R_f: 0.27 (hexanes/EtOAc 1:1).

M.p.: 134 – 136 °C.

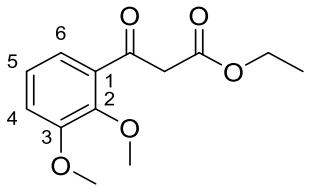
^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) = 8.44 (d, *J* = 4.9 Hz, 1H, 6-H), 7.58 – 7.52 (m, 2H, 2'-H and 6'-H), 7.46 – 7.38 (m, 3H, 3'-H and 4'-H and 5'-H), 7.12 (d, *J* = 4.9 Hz, 1H, 5-H), 4.62 (s, 2H, C<u>H</u>$_2$OH), 2.51 (s, 3H, CH$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): *δ* (ppm) = 159.7 (C-2), 148.6 (C-6), 140.3 (C-1'), 131.7 (C-3), 129.2 (C-2' and C-6'), 128.3 (C-3' and C-5'), 128.3 (C-4'), 124.8 (C-5), 59.6 (CH$_2$), 19.2 (CH$_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3208, 1593, 1440, 1403, 1319, 1015, 864, 826, 757, 704.

HRMS (EI): *m*/*z* = [M-H]$^{\bullet-}$ calcd for $C_{13}H_{12}NO^{\bullet-}$: 198.0919; found 198.0912.

Ethyl 3-(2,3-dimethoxyphenyl)-3-oxopropanoate (277)



$C_{13}H_{16}O_5$

M = 252.2660 g/mol

This compound was prepared from

a) 2,3-dimethoxybenzaldehyde (**275**, 19.9 g, 120 mmol), ethyl diazoacetate (15% in toluol, 110 mL, 144 mmol) and $SnCl_2$ (5.69 g, 30.0 mmol) in accordance with **General procedure R1**. Purification by FCC afforded the product **277** as an amber colored oil of inseparable of keto-enol tautomers (11.6 g, 45.8 mmol, 38%).

b) 2,3-dimethoxybenzaldehyde (**275**, 332 mg, 2.00 mmol), ethyl diazoacetate (15% in toluol, 1.68 mL, 2.40 mmol) and $NbCl_5$ (135 mg, 0.500 mmol) in accordance with **General procedure R1**. Purification by FCC afforded the product **277** as an amber colored oil of inseparable of keto-enol tautomers (174 mg, 0.690 mmol, 35%).

c) 2,3-dimethoxybenzoic acid (**276**, 20.0 g, 110 mmol), $SOCl_2$ (80.2 mL, 1.10 mol), and ethyl potassium malonate (26.5 g, 154 mmol), $MgCl_2$ (18.0 g, 187 mmol) and NEt_3 (53.7 mL, 385 mmol) in accordance with **General procedure R2**. Purification by FCC afforded product **277** as an amber colored oil of inseparable of keto-enol tautomers (18.5 g, 73.3 mmol, 67%).

β-Ketoester:

R_f: 0.49 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.29 (dd, J = 6.2, 3.3 Hz, 1H, 4-H or 6-H), 7.12 – 7.10 (m, 2H, 5-H and 4-H or 6-H), , 4.16 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 3.95 (s, 2H, $COCH_2CO$), 3.90 (s, 3H, 2-OCH_3), 3.88 (s, 3H, 3-OCH_3), 1.24 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 193.9 ($\underline{C}OCH_2CO$), 167.8 $COCH_2\underline{C}O$), 153.0 (C-3), 149.2 (C-2), 131.6 (C-1), 123.8 (C_{arom}), 121.1 (C_{arom}), 116.8 (C_{arom}), 61.1 (2-OCH_2), 61.0 ($CO\underline{C}H_2CH_3$), 56.0 (3-OCH_3), 49.9 ($CO\underline{C}H_2CO$), 13.9 ($COCH_2\underline{C}H_3$).

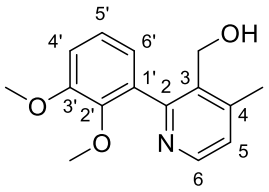
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2982, 2940, 1736, 1678, 1581, 1477, 1324, 1263, 1228, 1086, 999, 794, 748.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{13}H_{16}NO_5^{\bullet+}$: 252.0998; found 252.0992.

Enol:

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 12.64 (s, 0.10H, OH), 5.87 (s, 0.11H, vinyl-H), 4.25 (q, J = 7.2 Hz, 0.24H, $OC\underline{H}_2CH_3$), 3.87 (s, 0.41H, OCH_3), 3.81 (s, 0.36H, OCH_3), 1.32 (t, J = 7.1 Hz, 0.34H, $OCH_2C\underline{H}_3$).

(2-(2,3-Dimethoxyphenyl)-4-methylpyridin-3-yl)methanol (278)



$C_{15}H_{17}NO_3$

M = 259.3050 g/mol

This compound was prepared in accordance with **General procedure Q** from ester **178** (452 mg, 1.50 mmol) and LAH (114 mg, 3.00 mmol). Purification by FCC afforded the product **278** as a white solid (261 mg, 1.00 mmol, 67%).

R_f: 0.40 (EtOAc).

M.p.: 137 – 138 °C.

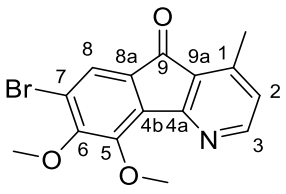
^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ (ppm) = 8.36 (d, J = 4.9 Hz, 1H, 6-H), 7.23 – 7.20 (m, 1H, 5-H), 7.11 – 7.09 (m, 2H, 5‘-H and 6‘-H), 6.82 (dd, J = 6.2, 2.9 Hz, 1H, 4‘-H), 4.69 (t, J = 4.8 Hz, 1H, OH), 4.39 (dd, J = 11.7, 5.2 Hz, 1H, $C\underline{H}_2OH$), 4.19 (dd, J = 11.7, 4.3 Hz, 1H, $C\underline{H}_2OH$), 3.84 (s, 3H, 3‘-OCH_3), 3.47 (s, 3H, 2‘-OCH_3), 2.45 (s, 3H, CH_3).

^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ (ppm) = 155.9 (C-2), 152.3 (C-3’), 147.4 (C-6), 147.4 (C-4), 146.1 (C-2’), 135.1 (C-1’), 133.3 (C-3), 124.7 (C-5), 123.5 (C-5’ or C-6’), 122.2 (C-4’), 112.5 (C-5’ or C-6’), 60.2 (2’-OCH_3), 58.0 (CH_2OH), 55.7 (3‘-OCH_3), 18.7 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3207, 2882, 1592, 1440, 1402, 1319, 1015, 864, 826, 857, 703.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{17}NO_3^{\bullet+}$: 259.1208; found 259.1213.

7-Bromo-5,6-dimethoxyonychine (283)



$C_{15}H_{12}BrNO_3$

M = 334.1690 g/mol

This compound was prepared in accordance with **General procedure F** from azafluorenone **181** (102 mg, 0.400 mmol) and NBS (75.5 mg, 0.420 mmol). Purification by FCC afforded the product **283** as a yellow solid (92.0 mg, 0.273 mmol, 69%).

R_f: 0.24 (hexanes/EtOAc 4:1).

M.p.: 155 – 156 °C.

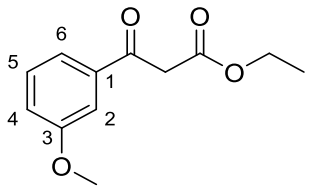
^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 8.47 (d, J = 5.3 Hz, 1H, 3-H), 7.64 (s, 1H, 8-H), 6.99 (dd, J = 5.3, 0.8 Hz, 1H, 2-H), 4.06 (s, 3H, 5-OCH_3), 4.01 (s, 3H, 6-OCH_3), 2.60 (d, J = 0.7 Hz, 3H, CH_3).

^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 191.1 (C-9), 164.3 (C-4a), 157.4 (C-6), 153.5 (C-3), 150.3 (C-5), 147.8 (C-1), 135.2 (C-4b), 132.3 (C-8a), 126.4 (C-9a), 125.8 (C-2), 124.2 (C-8), 120.0 (C-7), 62.3 (5-OCH_3), 61.7 (6-OCH_3), 17.5 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2915, 2847, 1703, 1557, 1464, 1404, 1354, 1269, 1236, 1080, 1041, 968.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{12}{}^{79}BrNO_3{}^{\bullet+}$: 333.0001; found 333.0009.

Ethyl 3-(3-methoxyphenyl)-3-oxopropanoate (286)



$C_{12}H_{14}O_4$

M = 222.2400 g/mol

This compound was prepared from

a) 3-methoxybenzaldehyde (**349**, 11.6 g, 82.3 mmol), $SnCl_2$ (3.82 mg, 20.2 mmol) and ethyl diazoacetate (15% in toluene, 75.0 mL, 107 mmol) in accordance with **General procedure R1**. Purification by FCC afforded the product **286** as a yellow oil of inseparable of keto-enol tautomers (6.90 mg, 31.0 mmol, 38%).
b) 3-methoxybenzoic acid (**285**, 13.8 g, 90.0 mmol), $SOCl_2$ (38.1 mL, 450 mmol), ethyl potassium malonate (20.1 g, 117 mmol), $MgCl_2$ (14.7 g, 153 mmol) and NEt_3 (43.9 mL,

315 mmol) in accordance with **General procedure R2**. Purification by FCC gave the product **286** as a white solid (16.4 g, 73.7 mmol, 82%).

β-Ketoester:

R_f: 0.47 (hexanes/EtOAc 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.53 – 7.47 (m, 2-H and 6-H), 7.41 – 7.36 (m, 1H, 5-H), 7.14 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H, 4-H), 4.21 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 3.97 (s, 2H, $COCH_2COO$), 3.85 (s, 3H, OCH_3), 1.26 (t, *J* = 7.1 Hz, 3H, $COOCH_2CH_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 192.5 ($COCH_2COO$), 167.6 ($COCH_2COO$), 160.1 (C-3), 137.5 (C-1), 129.9 (C-5), 121.3 (C-2 or C-6), 120.5 (C-4), 112.6 (C-2 or C-6), 61.6 ($COOCH_2CH_3$), 55.6 (OCH_3), 46.3 ($COCH_2COO$), 14.2 ($COOCH_2CH_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2982, 1735, 1684, 1597, 1582, 1431, 1319, 1273, 1247, 1224, 1144, 1029, 870, 786, 684.

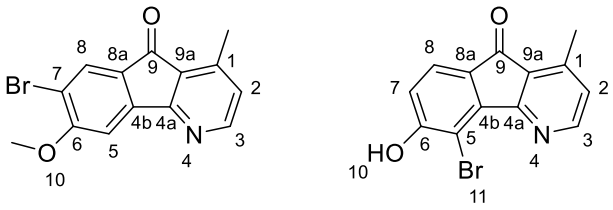
HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{12}H_{14}O_4^{\bullet+}$: 222.0892; found 222.0884.

Enol:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.57 (s, 0.16H, OH), 5.65 (s, 0.17H, vinyl-H) 4.28 (q, *J* = 7.1 Hz, 0.30H), 1.34 (1H, t, J=7.1 Hz).

Literature known compound.[283]

7-Bromo-6-methoxyonychine (288) and **5-bromo-6-hydroxyonychine (289)**



$C_{14}H_{10}BrNO_2$, $C_{18}H_8BrNO_2$

M = 304.1430 g/mol, M = 290.116 g/mol

These compounds were prepared in accordance with **General procedure F** from azafluorenone (**91**, 49.6 mg, 0.220 mmol) and NBS (43.1 mg, 0.242 mmol). Purification by FCC afforded the product **288** as yellow solid (10.3 mg, 0.0349 mmol, 15%). The compound **288** was accompanied by compound **289**, obtained as a yellow solid (25.0 mg, 0.0862 mmol, 39%).

7-Bromo-6-methoxyonychine (**288**):

R_f: 0.20 (hexanes/EtOAc 1:1).

M.p.: 212 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 8.39 (d, *J* = 5.3 Hz, 1H, 3-H), 7.86 (s, 1H, 8-H), 7.37 (s, 1H, 5-H), 6.99 (d, *J* = 5.3 Hz, 1H, 2-H), 4.05 (s, 3H, OCH_3), 2.62 (s, 3H, CH_3).

^{13}C NMR(101 MHz, $CDCl_3$): 190.9 (C-9), 164.1 (C-4a), 161.5 (C-6), 152.6 (C-3), 147.6 (C-1), 144.9 (C-4b), 129.3 (C-8), 128.5 (C-8a), 126.6 (C-9a), 126.5 (C-2), 114.0 (C-7), 104.2 (C-5), 57.1 (OCH_3), 17.3 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1708, 1603, 1564, 1462, 1352, 1257, 1240, 1149, 1031, 904, 834, 798, 681.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{10}{}^{79}BrNO_2{}^{\bullet+}$: 302.9895; found 302.9890.

5-Bromo-6-hydroxyonychine (**289**):

R_f: 0.29 (hexanes/EtOAc 2:1).

M.p.: 192 °C.

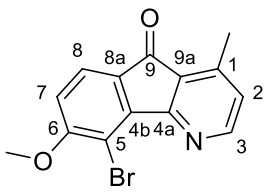
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.81 (bs, 1H, OH), 8.58 (d, *J* = 5.3 Hz, 1H, 3-H), 7.53 (d, *J* = 5.9 Hz, 1H, 8-H), 7.02 (d, *J* = 5.2 Hz, 2-H), 6.79 (bs, 1H, 7-H), 2.64 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 195.1 (C-9), 164.4 (C-4a), 156.8 (C-6), 153.0 (C-3), 147.9 (C-1), 142.6 (C-8), 139.3 (C-4b), 126.6 (C-9a), 125.9 (C-2), 121.9 (C-5), 119.8 (C-8a), 107.2 (C-7), 17.5 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3332, 2922, 1682, 1609, 1592, 1562, 1418, 1290, 1269, 1249, 1154, 1102, 927, 818, 806.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{14}H_8{}^{79}BrNO_2{}^{\bullet+}$: 288.9738; found 288.9733.

5-Bromo-6-methoxyonychine (290)



$C_{14}H_{10}BrNO_2$

M = 304.1430 g/mol

This compound was prepared in accordance with from

a) azafluorenone **289** (29.0 mg, 0.100 mmol), MeI (0.00685 mL, 0.110 mmol) and K_2CO_3 (15.0 mg, 0.150 mmol) following **General procedure O**. Purification by FCC afforded the product **290** as yellow solid (28.0 mg, 0.0921 mmol, 92%).
b) ester **305** (1.12 g, 3.20 mmol) and PPA (10.0 g) following **General procedure C**. Purification by FCC afforded the product **290** as yellow solid (200 mg, 0.658 mmol, 21%).

R_f: 0.29 (hexanes/EtOAc 4:1).

M.p.: 213 – 214 °C.

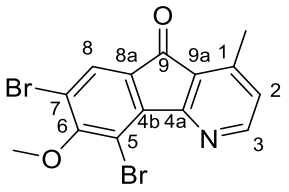
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 8.51 (d, J = 5.3 Hz, 1H, 3-H), 7.64 (d, J = 8.1 Hz, 1H, 8-H), 7.04 (dd, J = 5.2, 0.7 Hz, 1H, 2-H), 6.88 (d, J = 8.2 Hz, 1H, 7-H), 3.99 (s, 3H, OCH_3), 2.62 (d, J = 0.7 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 191.2 (C-9), 164.8 (C-4a), 162.4 (C-6), 152.6 (C-3), 147.7 (C-1), 142.9 (C-4b), 130.2 (C-8a), 127.7 (C-9a), 126.6 (C-2), 124.5 (C-8), 112.3 (C-7), 107.6 (C-5), 57.6 (OCH_3), 17.6 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2921, 2850, 1709, 1557, 1464, 1419, 1351, 1263, 1185, 1048, 907, 844.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{14}H_{10}{}^{79}BrO_2$ $[M]^{\bullet+}$: 302.9895; found 302.9890.

5,7-Dibromo-6-methoxyonychine (291)



$C_{14}H_9Br_2NO_2$

M = 383.0390 g/mol

This compound was prepared in accordance with **General procedure F** from azafluorenone **91** (185 mg, 0.820 mmol) and NBS (302 mg, 1.68 mmol). Purification by FCC afforded the product **291** as a yellow solid (81.0 mg, 0.211 mmol, 26%).

R_f: 0.43 (hexanes/EtOAc 8:1).

M.p.: 216 °C.

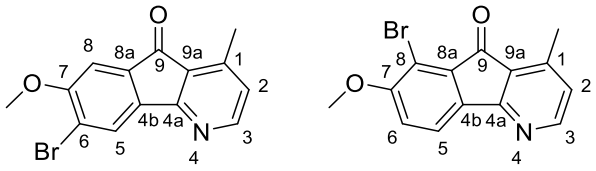
^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 8.53 (d, J = 5.3 Hz, 1H, 3-H), 7.83 (s, 1H, 8-H), 7.07 (dd, J = 5.3, 0.8 Hz, 1H, 2-H), 3.97 (s, 3H, OCH_3), 2.62 (d, J = 0.7 Hz, 3H, CH_3).

^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 190.3 (C-9), 164.6 (C-4a), 160.5 (C-6), 153.1 (C-3), 148.4 (C-1), 142.2 (C-4b), 133.6 (C-8a and C-9a), 128.1 (C-8), 126.7 (C-2), 120.5 (C-7), 114.2 (C-5), 61.4 (6-OCH_3), 17.7 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2922, 2853, 1707, 1590, 1567, 1447, 1383, 1370, 1338, 1268, 1252, 1230, 1175, 1154, 1125, 1072, 1031, 988, 962, 910, 895, 855, 834, 800, 763, 746, 722, 697.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{14}H_9{}^{79}Br_2NO_2{}^{\bullet+}$: 380.9000; found: 380.8994.

6-Bromo-7-methoxyonychine (292) and **8-bromo-7-methoxyonychine (293)**



$C_{14}H_{10}BrNO_2$

M = 304.1430 g/mol

This compound was prepared in accordance with **General procedure F** from azafluorenone **95** (85.6 mg, 0.380 mmol) and NBS (67.6 mg, 0.380 mmol). Purification by FCC afforded 6-bromo-7-methoxyonychine (**292**, 105 mg, 0.345 mmol, 91%) as yellow solid. The compound **292** was accompanied by its 8-bromo regioisomer **293**, obtained as a yellow solid (2.95 mg, 0.00970 mmol, 3%).

<u>6-Bromo-7-methoxyonychine (**292**):</u>

R_f: 0.54 (hexanes/EtOAc 4:1 + 1% AcOH).

M.p.: °C.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1718, 1705, 1588, 1561, 1464, 1364, 1263, 1252, 1242, 1056, 1029, 973, 893, 852, 826, 799, 738, 659.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.35 (d, J = 5.3 Hz, 1H, 3-H), 8.00 (s, 1H, 5-H), 7.21 (s, 1H, 8-H), 6.90 (dd, J = 5.4, 0.7 Hz, 1H, 2-H), 3.98 (s, OCH_3), 2.60 (d, J = 0.7 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 192.5 (C-9), 164.7 (C-4a), 158.4 (C-7), 153.0 (C-3), 147.7 (C-1), 136.6 (C-4b), 135.7 (C-8a), 126.3 (C-5), 126.0 (C-9a), 125.5 (C-2), 119.2 (C-6), 106.9 (C-8), 56.9 (OCH_3), 17.5 (CH_3).

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}{}^{79}Br_2NO_2{}^{\bullet+}$: 302.9895; found 302.9890.

8-Bromo-7-methoxyonychine (**293**):

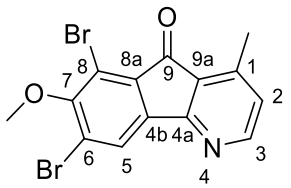
R_f: 0.21 (hexanes/EtOAc 4:1 + 1% AcOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.39 (d, *J* = 5.2 Hz, 1H, 3-H), 7.76 (d, *J* = 8.1 Hz, 1H, 5-H), 7.03 (d, *J* = 8.1 Hz, 1H, 6-H), 6.94 (d, *J* = 5.3 Hz, 1H, 2-H), 3.98 (s, 3H, OCH_3), 2.63 (s, 3H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 191.0 (C-9), 163.6 (C-4a), 158.8 (C-7), 153.2 (C-3), 148.1 (C-1), 137.2 (C-4b), 133.7 (C-8a), 125.9 (C-9a), 125.6 (C-2), 120.7 (C-5), 116.1 (C-8), 110.6 (C-6), 57.1 (OCH_3), 17.5 (CH_3).

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{11}{}^{79}Br_2NO_2{}^{\bullet+}$: 302.9895; found 302.9890.

6,8-Dibromo-7-methoxyonychine (294)



$C_{14}H_9Br_2NO_2$

M = 383.0390 g/mol

This compound was prepared in accordance with **General procedure F** from azafluorenone **95** (101 mg, 0.450 mmol) and NBS (160 mg, 0.900 mmol). Purification by FCC afforded the product **294** as yellow solid (131 mg, 0.342 mmol, 76%).

R_f: 0.49 (hexanes/EtOAc 4:1 + 1% AcOH).

M.p.: 212 – 213 °C.

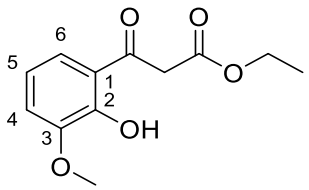
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2923, 1718, 1554, 1451, 1360, 1249, 1023, 952, 802, 767, 738.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.43 (d, *J* = 5.3 Hz, 1H, 3-H), 8.02 (s, 1H, 5-H), 7.01 (dd, *J* = 5.2, 0.8 Hz, 1H, 2-H), 3.95 (s, 3-H, OCH_3), 2.64 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): *δ* (ppm) = 189.8 (C-9), 162.1 (C-4a), 157.0 (C-7), 153.4 (C-3), 148.3 (C-1), 141.5 (C-4b), 132.7 (C-8a), 126.5 (C-2), 126.1 (C-9a), 125.4 (C-8), 124.9 (C-5), 116.5 (C-6), 61.2 (OCH_3), 17.5 (CH_3).

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{14}H_9{}^{79}Br_2NO_2{}^{\bullet+}$. 380.9000, found 380.8995.

ethyl 3-(2-hydroxy-3-methoxyphenyl)-3-oxopropanoate (296)



$C_{12}H_{14}O_5$

M = 238.2390 g/mol

This compound was prepared in accordance with **General procedure R1** from aldehyde **298** (7.74 g, 32.2 mmol), ethyl diazoacetate (15% in toluol, 29.3 mL, 41.9 mmol) and $SnCl_2$ (1.50 g, 7.89 mmol). Purification by FCC afforded the product as a pale-yellow oil (2.16 g, 9.05 mmol, 28%).

R_f: 0.33 (hexanes/EtOAc 4:1).

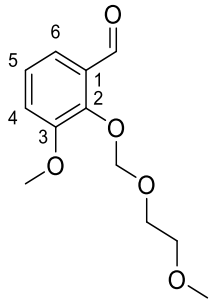
^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ (ppm) = 11.08 (s, 1H, OH), 7.36 (dd, *J* = 8.2, 1.4 Hz, 1H, 6-H), 7.24 (dd, *J* = 8.0, 1.4 Hz, 1H, 4-H), 6.89 (t, *J* = 8.0 Hz, 1H, 5-H), 4.14 (s, 2H, $COCH_2COO$), 4.11 (q, *J* = 7.1 Hz, 2H, $COCH_2CH_3$), 3.82 (s, 3H, OCH_3), 1.18 (t, *J* = 7.1 Hz, $COCH_2CH_3$).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 197.8 ($COCH_2COO$), 168.0 ($COCH_2COO$), 150.8 (C-2), 148.8 (C-3), 122.1 (C-6), 121.6 (C-1), 119.2 (C-5), 117.8 (C-4), 61.1 ($COOCH_2CH_3$), 56.5 (OCH_3), 48.0 ($COCH_2CO$), 14.5 ($COOCH_2CH_3$).

IR (ATR): 2981, 1734, 1638, 1456, 1252, 1017, 734.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{12}H_{14}O_5{}^{\bullet+}$: 238.0841; found 238.0833.

3-Methoxy-2-((2-methoxyethoxy)methoxy)benzaldehyde (298)



$C_{12}H_{16}O_5$

M = 240.2550 g/mol

This compound was prepared in accordance with **General procedure K** from 2-hydroxy-3-methoxybenzaldehyde (**295**, 5.08 g, 33.4 mmol, 1.00 equiv.), NaH (1.20 g, 50.1 mmol, 1.50 equiv.) and MEMCl (5.34 mL, 46.8 mmol, 1.40 equiv.). Purification by FCC afforded the product **298** as a cloudy, pale-yellow oil (5.28 mg, 22.0 mmol, 66%).

R_f: 0.11 (hexanes/EtOAc 8:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 10.43 (d, J = 0.6 Hz, 1H, CHO), 7.39 (dd, J = 5.6, 3.8 Hz, 1H, 6-H), 7.19 – 7.17 (m, 2H, 4-H and 5-H), 5.29 (s, OCH_2O), 3.88 (s, 3H, OCH_3), 3.87 – 3.84 (m, 2H, $OC\underline{H}_2CH_2OCH_3$), 3.52 – 3.48 (m, 2H, $OCH_2C\underline{H}_2OCH_3$), 3.31 (s, 3H, $OCH_2CH_2OC\underline{H}_3$).

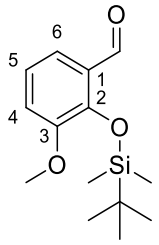
^{13}C NMR (126 MHz, CD_2Cl_2): δ (ppm) = 190.6 (CHO), 153.0 (C-3), 149.6 (C-2), 130.9 (C-1), 124.9 (C-4 or C-5), 119.2 (C-6), 118.2 (C-4 or C-5), 98.7 (OCH_2O), 72.0 ($OCH_2\underline{C}H_2OCH_3$), 70.0 ($O\underline{C}H_2CH_2OCH_3$), 59.1 ($OCH_2CH_2O\underline{C}H_3$), 56.4 ($OCH_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2883, 1689, 1584, 1483, 1458, 1380, 1317, 1244, 1214, 1103, 1062, 933, 910, 848, 808, 780, 750.

HRMS (ESI): m/z = $[M+Na]^+$ calcd for $C_{12}H_7NONa^+$ 263.0895; found 263.0889.

Literature known compound.[284]

2-((*tert*-Butyldimethylsilyl)oxy)-3-methoxybenzaldehyde (299)



$C_{14}H_{22}O_3Si$

M = 266.4120 g/mol

This compound was prepared in accordance with **General procedure J** from phenol 2-hydroxy-3-methoxybenzaldehyde (**295**, 5.00 g, 32.9 mmol), imidazole (5.59 g, 82.1 mmol) and TBSCl (6.93 g, 46.0 mmol). Purification by FCC afforded the product **299** as a pale-yellow oil (5.89 g, 22.1 mmol, 67%).

R_f: 0.33 (hexanes/EtOAc 8:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 10.49 (d, J = 0.9 Hz, 1H, CHO), 7.33 (dd, J = 7.9, 1.7 Hz, 1H, 6-H), 7.09 (dd, J = 8.0, 1.6 Hz, 1H, 4-H), 6.97 (td, J = 7.9, 0.9 Hz, 1H, 5-H), 3.83 (s, 3H, OCH_3), 1.01 (s, 9H, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.22 (s, 6H, $Si(C\underline{H}_3)_2C(CH_3)_3$).

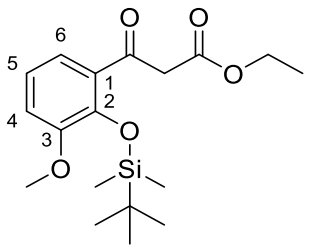
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 190.4 (CHO), 151.3 (C-3), 149.5 (C-2), 128.3 (C-1), 121.5 (C-5), 119.2 (C-6), 117.3 (C-4), 55.6 (OCH_3), 26.1 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 19.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), -4.1 ($Si(\underline{C}H_3)_2C(CH_3)_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2958, 2933, 2856, 1678, 1598, 1486, 1455, 1386, 1245, 1070, 911, 808, 774, 733.

HRMS (EI): m/z = $[M–CH_3]^{\bullet+}$ calcd for $C_{13}H_{22}O_3Si^{\bullet+}$ 251.1103; found 251.1095.

Literature known compound.[285]

Ethyl 3-(2-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)-3-oxopropanoate (300)



$C_{18}H_{28}O_5Si$

M = 352.5020 g/mol

This compound was prepared in accordance with **General procedure R1** from aldehyde **299** (1.07 g, 4.00 mmol), $SnCl_2$ (190 mg, 0.980 mmol) and ethyl diazoacetate (15% in toluene, 3.65 mL, 5.20 mmol). Purification by FCC afforded the product **300** as a yellow oil of inseparable of keto-enol tautomers (833 mg, 2.36 mmol, 59%).

β-Ketoester

R_f: 0.58 (hexanes/EtOAc 10:1).

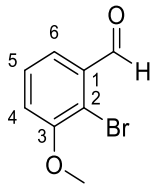
^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 7.03 – 6.97 (m, 2H, H_{arom}), 6.96 – 6.93 (m, 1H, H_{arom}), 4.13 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 3.99 (s, 2H, OCH_2O)), 3.81 (s, 3H, OCH_3), 1.21 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 0.97 (s, 9H, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.15 (s, 6H, $Si(C\underline{H}_3)_2C(CH_3)_3$).

HRMS (ESI): *m*/*z* = $[M+Na]^{\bullet+}$ calcd for $C_{18}H_{28}O_5SiNa^+$: 375.1604; found 375.1599.

Enol:

^{1}H NMR (500 MHz, CD_2Cl_2): δ (ppm) = 12.42 (s, 0.25H, OH), 7.15 (dd, *J* = 6.6, 2.9 Hz, 0.23H, H_{arom}), 5.70 (s, 0.24 H, vinyl-H), 4.24 (q, *J* = 7.1 Hz, 0.51H, $OC\underline{H}_2CH_3$), 3.80 (s, 1.17H, OCH_3), 1.29 (t, *J* = 7.1 Hz, 0.81H, $OCH_2C\underline{H}_3$), 0.95 (s, 2.25H, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.13 (s, 1.45H, $Si(C\underline{H}_3)_2C(CH_3)_3$).

2-Bromo-3-methoxybenzaldehyde (303)



$C_8H_7BrO_2$

M = 215.0460 g/mol

This compound was prepared in accordance with **General procedure O** from 2-bromo-3-hydroxybenzaldehyde (**302**, 9.75 g, 48.0 mmol), K_2CO_3 (14.4 g, 144 mmol) and MeI (5.98 mL, 96.0 mmol). Purification by FCC afforded the product **303** as a white solid (10.1 g, 47.1 mmol, 98%).

R_f: 0.51 (hexanes/EtOAc 8:1).

M.p.: 69 – 70 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 10.41 (d, *J* = 0.8 Hz, 1H, CHO), 7.49 (dd, *J* = 7.7, 1.6 Hz, 1H, 4-H or 6-H), 7.40 (td, *J* = 7.9, 0.8 Hz, 1H, 5-H), 7.17 (dd, *J* = 8.1, 1.5 Hz, 1H, 4-H or 6-H), 3.94 (s, 3H, OCH_3).

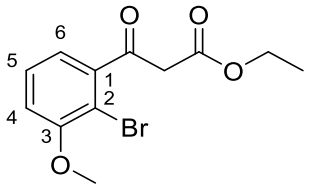
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 192.6 (CO), 157.0 (C-3), 135.4 (C-1), 129.0 (C-5), 121.7 (C-4 or C-6), 117.6 (C-4 or C-6), 117.4 (C-2), 57.2 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2970, 1684, 1564, 1467, 1429, 1382, 1301, 1268, 1237, 1057, 1030, 900, 784.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_8H_7{}^{79}BrO_2{}^{\bullet+}$: 213.9629; found 213.9622.

Literature known compound.[286]

Ethyl 3-(2-bromo-3-methoxyphenyl)-3-oxopropanoate (304)



$C_{12}H_{13}BrO_4$

M = 301.1360 g/mol

This compound was prepared in accordance with **General procedure R1** from aldehyde **303** (10.5 g, 49.0 mmol), $SnCl_2$ (2.28 g, 12.0 mmol) and ethyl diazoacetate (15% in toluene, 44.7 mL, 63.7 mmol). Attempt at purification by FCC afforded the crude product **304** as a yellow oil of inseparable of keto-enol tautomers among unidentified side-products (9.95 g).

β-Ketoester:

R_f: 0.35 (hexanes/EtOAc 8:1).

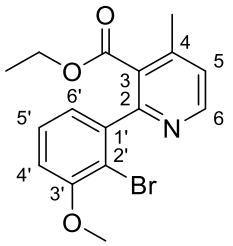
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.34 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.01 (ddd, *J* = 13.6, 8.0, 1.3 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 3.99 (s, 2H, OCH_2O), 3.92 (s, 3H, OCH_3), 1.25 (td, *J* = 7.1, 0.8 Hz, 3H, $OCH_2C\underline{H}_3$).

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{12}H_{13}{}^{79}BrO_4{}^{\bullet+}$: 299.9997; found 299.9992.

Enol:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.40 (d, *J* = 0.7 Hz, 0.29H, OH), 5.39 (s, 0.21H, vinyl-H), 4.32 – 4.23 (m, 0.72H, $OC\underline{H}_2CH_3$), 3.92 (s, 1.16H, OCH_3), 1.34 (td, *J* = 7.1, 0.7 Hz, 1.00H, $OCH_2C\underline{H}_3$).

Ethyl 2-(2-bromo-3-methoxyphenyl)-4-methylnicotinate (305)



$C_{16}H_{16}BrNO_3$

M = 350.2120 g/mol

This compound was prepared in accordance with **General procedure E** from crude β-ketoester **304** (9.45 g, 31.5 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 3.15 mL, 6.93 mmol), crotonaldehyde (3.91 mL, 47.3 mmol) and hydroxylammonium chloride (7.22 g, 104 mmol). Purification by FCC afforded the product **305** as a yellow oil (3.01 g, 8.59 mmol, 18% over two steps).

R_f: 0.37 (hexanes/EtOAc 2:1).

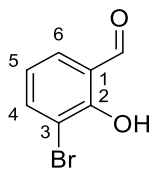
^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 8.55 (d, J = 5.1 Hz, 1H, 6-H), 7.31 (dd, J = 8.3, 7.6 Hz, 1H, 5'-H), 7.22 (dd, J = 5.1, 0.8 Hz, 1H, 5-H), 6.96 (dd, J = 8.3, 1.4 Hz, 1H, 4'-H or 6'-H), 6.86 (dd, J = 7.6, 1.4 Hz, 1H, 4'-H or 6'-H), 4.02 (q, J = 7.1 Hz, 1H, $COOC\underline{H}_2CH_3$), 3.92 (s, 3H, OCH_3), 2.49 – 2.43 (s, 3H, CH_3), 0.93 (t, J = 7.1 Hz, 3H, $COOCH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 167.6 (COO), 157.4 (C-2), 156.7 (C-3'), 150.0 (C-6), 146.5 (C-4), 143.3 (C-1'), 130.1 (C-3), 128.3 (C-5'), 125.1 (C-5), 122.9 (C-4' or C-6'), 112.6 (C-2'), 112.0 (C-4' or C-6'), 61.7 ($COO\underline{C}H_2CH_3$), 57.0 (OCH_3), 20.1 (CH_3), 13.9 ($COOCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2978, 1720, 1567, 1426, 1265, 1244, 1125, 1056, 781.

HRMS (EI): m/z = $[M\text{-}C_2H_5]^{\bullet+}$ calcd for $C_{14}H_{11}{}^{79}BrO_3{}^{\bullet+}$: 319.9922; found 319.9925.

3-Bromo-2-hydroxybenzaldehyde (307)



$C_7H_5BrO_2$

M = 201.0190 g/mol

A flame-dried 3-neck flask was charged with $MgCl_2$ (20.2 g, 212 mmol) and paraformaldehyde (30.2 g, 954 mmol), followed by anhydrous THF (0.500 L) and NEt_3 (73.9 mL, 530 mmol). The resulting suspension was stirred at rt for 10 minutes before 2-bromophenol (**306**; 25.0 g, 141 mmol) was added and the reaction heated to reflux overnight. After completion of the reaction, the mixture was allowed to cool to room temperature and diluted with EtOAc (0.20 L). The organic phase was washed with diluted HCl (2 M, 3 x 0.10 L), dried with $MgSO_4$, and concentrated under reduced pressure to give the crude product **307** (28.3 g) as a yellow oil, which was used without further purification.

R_f: 0.30 (hexanes/DCM 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.62 (s, 1H, OH), 9.87 (s, 1H, CHO), 7.79 (dd, J = 7.9, 1.6 Hz, 1H, 4-H), 7.56 (dd, J = 7.7, 1.6 Hz, 1H, 6-H), 6.96 (t, J = 7.8 Hz, 1H, 5-H).

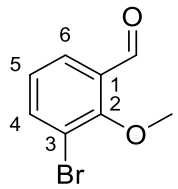
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 196.2 (CO), 158.3 (C-2), 140.2 (C-4), 133.1 (C-6), 121.5 (C-1), 120.9 (C-5), 111.4 (C-3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2856, 1645, 1438, 1384, 1291, 1216, 1171, 1128, 1073, 900, 778, 722, 668.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_7H_5{}^{79}BrO_2{}^{\bullet+}$: 199.9473; found 199.9475.

Literature known compound.[287]

3-Bromo-2-methoxybenzaldehyde (308)



$C_8H_7BrO_2$

M = 215.0460 g/mol

This compound was prepared in accordance with **General procedure O** from crude alcohol **307** (28.3 g), K_2CO_3 (46.6 g, 282 mmol) and MeI (9.66 mL, 155 mmol). Purification by FCC afforded the product **16** as a colorless solid (18.5 g, 86.0 mmol, 61% over two steps).

R_f: 0.48 (hexanes/EtOAc 12:1).

M.p.: 31 °C.

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 10.34 (d, *J* = 0.8 Hz, 1H, CHO), 7.83 (dd, *J* = 7.9, 1.7 Hz, 1H, 4-H), 7.78 (dd, *J* = 7.8, 1.7 Hz, 1H, 6-H), 7.15 (td, *J* = 7.8, 0.8 Hz, 1H, 5-H), 3.98 (s, 3H, OCH_3).

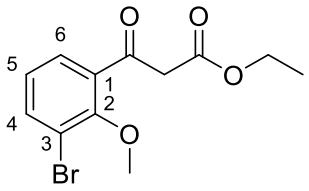
^{13}C NMR (101 MHz, CD_2Cl_2): 189.3 (CO), 160.5 (C-2), 139.8 (C-4), 131.5 (C-1), 128.2 (C-6), 126.2 (C-5), 118.6 (C-3), 63.8 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2952, 2889, 1682, 1586, 1459, 1420, 1387, 1236, 1166, 1117, 1069, 989, 853, 779.

HRMS (EI): *m*/*z* = $[M-H]^{\bullet-}$ calcd for $C_8H_7{}^{79}BrO_2{}^{\bullet-}$: 213.9629; found 213.9621.

Literature known compound.[288]

Ethyl 3-(3-bromo-2-methoxyphenyl)-3-oxopropanoate (309)



$C_{12}H_{13}BrO_4$

M = 301.1360 g/mol

This compound was prepared from

a) aldehyde **308** (18.1 g, 84.3 mmol), $SnCl_2$ (3.92 g, 20.7 mmol) and ethyl diazoacetate (15% in toluene, 76.8 mL, 110 mmol) in accordance with **General procedure R1**. Purification by FCC afforded product **309** as an amber colored oil of inseparable of keto-enol tautomers (8.76 g, 29.2 mmol, 35%).
b) from 3-bromo-2-methoxybenzoic acid (**348**, 706 mg, 2.83 mmol), $SOCl_2$ (2.06 mL, 28.3 mmol), ethyl potassium malonate (6.81 mg, 3.96 mmol), $MgCl_2$ (463 mg, 4.81 mmol) and NEt_3 (1.38 mL, 9.91 mmol) in accordance with **General procedure R2**. Purification by FCC afforded product **309** as an amber colored oil of inseparable of keto-enol tautomers (437 g, 1.45 mmol, 51%).

<u>β-Ketoester:</u>

R_f: 0.34 (hexanes/EtOAc 6:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.73 (dd, J = 7.9, 1.7 Hz, 1H, 4-H), 7.63 (dd, J = 7.8, 1.6 Hz, 1H, 6-H), 7.08 (t, J = 7.9 Hz, 1H, 5-H), 4.20 (q, J = 7.2 Hz, 2H, $COC\underline{H}_2CH_3$), 4.01 (s, 2H, $COCH_2CO$), 3.90 (s, 3H, OCH_3) , 1.25 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 193.9 ($\underline{C}OCH_2CO$), 167.4 ($COCH_2\underline{C}O$), 156.3 (C-2), 137.9 (C-4), 133.7 (C-1), 129.6 (C-6), 125.6 (C-5), 118.1 (C-3), 62.5 ($O\underline{C}H_2CH_3$), 61.4 (OCH_3), 49.1 ($CO\underline{C}H_2CO$), 14.1 ($OCH_2\underline{C}H_3$).

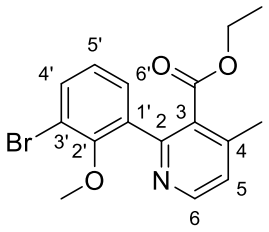
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2982, 1738, 1684, 1621, 1462, 1415, 1238, 1183, 1028, 993, 790, 756.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{12}H_{13}{}^{79}BrO_4{}^{\bullet+}$: 299.9997; found 299.9992.

Enol:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.62 (s, 0.31H, OH), 5.92 (s, 0.30H, OH vinyl), 4.27 (q, J = 7.1 Hz, 1H, $COC\underline{H}_2CH_3$), 3.83 (1H, s, OCH_3), 1.34 (1H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$).

Ethyl 2-(3-bromo-2-methoxyphenyl)-4-methylnicotinate (310)



$C_{16}H_{16}BrNO_3$

M = 350.2120 g/mol

This compound was prepared in accordance with **General procedure E** from β-ketoester **309** (16.3 g, 54.1 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 5.41 mL, 11.9 mmol), crotonaldehyde (5.83 mL, 70.3 mmol) and hydroxylammonium chloride (12.4 g, 179 mmol). Purification by FCC afforded the product **310** as a yellow oil (5.50 g, 15.7 mmol, 29%).

R_f: 0.35 (hexanes/EtOAc 3:1).

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 8.57 (d, J = 5.0 Hz, 1H, 6-H), 7.60 (dd, J = 8.0, 1.6 Hz, 1H, 4'-H), 7.30 (dd, J = 7.6, 1.6 Hz, 1H, 6'-H), 7.21 (dt, J = 4.9, 0.6 Hz, 1H, 5-H), 7.05 (t, J = 7.8 Hz, 1H, 5'-H), 4.06 (q, J = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.51 (s, 3H, OCH_3), 2.47 (d, J = 0.7 Hz, 3H, CH_3), 0.97 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$).

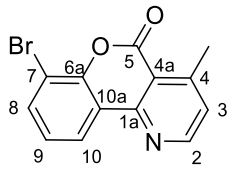
^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 167.7 (COO), 155.2 (C-2'), 154.9 (C-2), 150.2 (C-6), 146.9 (C-4), 136.7 (C-1'), 134.1 (C-4'), 130.6 (C-6'), 130.2 (C-3), 125.4 (C-5'), 125.1 (C-5),

117.7 (C-3'), 61.6 (OCH_3 or $O\underline{C}H_2CH_3$), 61.6 (OCH_3 or $O\underline{C}H_2CH_3$), 20.3 (CH_3), 13.9 ($OCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2978, 2935, 1721, 1577, 1448, 1415, 1273, 1239, 1127, 1094, 1064, 999, 783.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{16}H_{16}{}^{79}BrNO_3{}^{\bullet+}$: 349.0314; found 349.0307.

7-Bromo-4-methyl-5*H*-chromeno[4,3-*b*]pyridin-5-one (311)



$C_{13}H_8BrNO_2$

M = 290.1160 g/mol

This compound was prepared in accordance with **General procedure C** from ester **310** (45.5 mg, 0.130 mmol) and PPA (150 mg). Purification by FCC afforded the product **311** as a white solid (22.4 mg, 0.080 mmol, 62%).

R_f: 0.49 (hexanes/EtOAc 6:1).

M.p.: 190 – 191 °C.

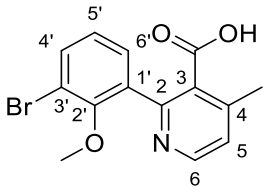
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.80 (d, *J* = 5.0 Hz, 1H, 2-H), 8.55 (dd, *J* = 8.0, 1.6 Hz, 1H, 8-H), 7.77 (dd, *J* = 7.9, 1.5 Hz, 1H, 10-H), 7.33 (dd, *J* = 4.9, 1.0 Hz, 1H, 3-H), 7.23 (t, *J* = 8.0 Hz, 1H, 9-H), 2.88 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 159.5 (COO), 154.6 (C-2), 153.8 (C-4), 152.5 (C-1a), 149.3 (C-6a), 135.7 (C-8), 127.3 (C-3), 125.3 (C-9), 124.8 (C-10), 121.2 (C-10a), 116.5 (C-4a), 110.3 (C-7), 23.0 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1733, 1592, 1556, 1470, 1430, 1220, 1078, 1064, 1027, 902, 782.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{13}H_8{}^{79}BrNO_2{}^{\bullet+}$: 288.9735; found 288.9731.

2-(3-Bromo-2-methoxyphenyl)-4-methylnicotinic acid (312)



$C_{14}H_{12}BrNO_3$

M = 322.1580 g/mol

This compound was prepared in accordance with **General procedure D** from ester **310** (4.90 g, 14.0 mmol) and KOH (2.99 g, 53.2 mmol). Purification by FCC afforded the product **312** as a white solid (3.33 g, 10.3 mmol, 74%).

R_f: 0.37 (EtOAc).

M.p.: 138 – 139 °C.

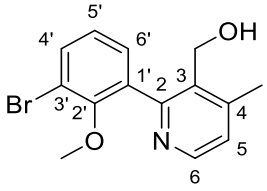
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 13.18 (s, 1H, COOH), 8.56 (d, J = 5.0 Hz, 1H, 6-H), 7.67 (dd, J = 8.0, 1.6 Hz, 1H, 4‘-H or 6‘-H), 7.39 – 7.37 (m, 1H, 5-H), 7.27 (dd, J = 7.6, 1.6 Hz, 1H, 4‘-H or 6‘-H), 7.12 (t, J = 7.8 Hz, 1H, 5‘-H), 3.47 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 168.5 (COOH), 154.2 (C-2’), 152.9 (C-2), 149.0 (C-6), 144.7 (C-4), 135.8 (C-1’), 133.3 (C-4’ or C-6’), 130.7 (C-3), 130.3 (C-4’ or C-6’), 125.1 (C-5’), 124.6 (C-5), 116.5 (C-3’), 60.8 (OCH_3), 19.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2921, 2852, 1711, 1452, 1416, 1243, 1137, 1070, 1002, 780, 735.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{14}H_{12}{}^{79}BrNO_3{}^{\bullet+}$: 321.0001; found 321.0005.

(2-(3-Bromo-2-methoxyphenyl)-4-methylpyridin-3-yl)methanol (313)



$C_{14}H_{14}BrNO_2$

M = 308.1750 g/mol

This compound was prepared in accordance with **General procedure S** from carboxylic acid **312** (677 mg, 2.10 mmol), dimethyl sulfide borane (2.0 M solution in THF, 3.15 mL, 6.30 mmol)

and trimethylborate (0.702 mL, 6.30 mmol). Purification by FCC afforded the product **313** as a white resin (253 mg, 0.821 mmol, 39%).

R_f: 0.24 (hexanes/EtOAc 1:1).

M.p.: 121 – 122 °C.

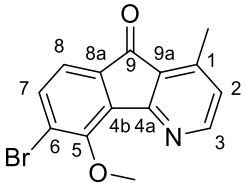
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 8.40 (d, J = 4.9 Hz, 1H, 6-H), 7.71 – 7.67 (m, 1H, 6'-H), 7.31 – 7.28 (m, 1H, 4-H), 7.27 (d, J = 5.0 Hz, 1H, 5-H), 7.17 – 7.12 (m, 1H, 5'-H), 4.79 (t, J = 4.8 Hz, 1H, OH), 4.43 (dd, J = 10.6, 5.0 Hz, 1H, C$\underline{H}_2$OH), 4.21 – 4.12 (m, 1H, C$\underline{H}_2$OH), 3.41 (s, 3H, OCH_3), 2.47 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 155.1 (C-2), 154.0 (C-2'), 147.7 (C-4), 147.6 (C-6), 136.2 (C-1'), 133.4 (C-3), 133.0 (C-6'), 130.7 (C-4'), 125.1 (C-5), 125.1 (C-5'), 116.5 (C-3'), 60.8 (OCH_3), 57.8 (CH_2OH), 18.7 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3220, 2937, 1735, 1585, 1452, 1414, 1238, 996, 833, 783, 755, 716.

HRMS (EI): m/z = $[M-H]^{\bullet-}$ calcd for $C_{14}H_{13}{}^{79}BrNO_2$ $[M-H]^{\bullet-}$: 306.0130; found 306.0125.

6-Bromo-5-methoxyonychine (314)



$C_{14}H_{10}BrNO_2$

M = 304.1430 g/mol

This compound was prepared in accordance with **General procedure A2** from pyridinemethanol **313** (148 mg, 0.480 mmol) and TBHP (5.5 M in decane, 0.349 mL, 1.92 mmol). Purification by FCC afforded the product **314** as a yellow solid (34.3 mg, 0.113 mmol, 23%).

R_f: 0.48 (hexanes/EtOAc 4:1).

M.p.: 157 – 158 °C.

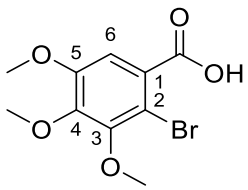
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.53 (d, J = 5.3 Hz, 1H, 3-H), 7.64 (d, J = 7.8 Hz, 1H, 7-H), 7.35 (d, J = 7.8 Hz, 1H, 8-H), 6.99 (dd, J = 5.3, 0.7 Hz, 1H, 2-H), 4.08 (s, 3H, OCH_3), 2.63 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 192.1 (C-9), 164.2 (C-4a), 153.4 (C-3), 153.0 (C-5), 147.8 (C-1), 136.3 (C-8a), 135.8 (C-7), 135.1 (C-4b), 127.2 (C-6), 126.1 (C-9a), 125.7 (C-2), 120.5 (C-8), 61.9 (OCH_3), 17.6 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2924, 1709, 1586, 1555, 1457, 1421, 1353, 1269, 1236, 1066, 1031, 950, 844, 779.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{14}H_{10}{}^{79}BrNO_2{}^{\bullet+}$: 302.9895; found 302.9899.

2-Bromo-3,4,5-trimethoxybenzoic acid (316)



$C_{10}H_{11}BrO_5$

M = 291.0970 g/mol

This compound was prepared in accordance with **General procedure N** with 3,4,5-trimethoxybenzaldehyde (**315**, 12.7 g, 60.0 mmol, 1.00 equiv.) and NBS (11.7 g, 66.0 mmol, 1.10 equiv.), using MeCN (0.50 L) as the solvent to give the crude product **316** as a white solid (12.2 g, 41.9 mmol, 70%). The crude product was used without further purification.

R_f: 0.31 (hexanes/EtOAc 6:1).

M.p.: 33 – 34 °C.

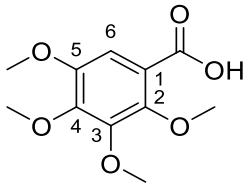
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.40 (s, 1H, 6-H), 3.97 (s, 3H, 4-OCH_3), 3.91 (s, 3H, 3-OCH_3 or 5-OCH_3), 3.90 (s, 3H, 3-OCH_3 or 5-OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 170.2 (CO), 152.4 (C-3 or C-5), 151.9 (C-3 or C-5), 147.2 (C-4), 125.4 (C-1), 111.4 (C-6), 111.1 (C-2), 61.3 (3-OCH_3 or 5-OCH_3), 61.2 (4-OCH_3), 56.4 (3-OCH_3 or 5-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2942, 1731, 1565, 1483, 1426, 1383, 1334, 1215, 1171, 1103, 1031, 1004, 987, 902, 777, 734.

HRMS (ESI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{10}H_{11}{}^{79}BrO_5{}^{\bullet+}$: 289.9790; found 289.9776.

2,3,4,5-Tetramethoxybenzoic acid 38 (317)



$C_{11}H_{14}O_6$

M = 242.2270 g/mol

2-bromo-3,4,5-trimethoxybenzoic acid (**316**, 11.6 g, 40.0 mmol, 1.00 equiv.) was added to a stirred solution of sodium metal (3.22 g, 140 mmol, 3.50 equiv.) dissolved in anhydrous methanol (0.20 L). After the acid had dissolved, CuBr (574 mg, 4.00 mmol, 0.100 equiv.) was added and the resulting mixture was refluxed for 18 h. The mixture was cooled, fltered through a bed of celite, and concentrated *in vacuo*. The residue was dissolved in water (0.20 L) and acidified to pH = 3 with concentrated HCl. The solution was extracted with EtOAc (3 x 50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by FCC afforded the product **317** as a white solid (9.44 g, 39.0 mmol, 97%).

R_f: 0.50 (hexanes/EtOAc 1:1).

M.p.: 87 – 88 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.30 (s, 1H, COOH), 7.41 (s, 1H, 6-H), 4.08 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3).

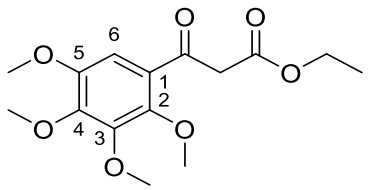
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 165.1 (COO), 150.2 ($\underline{C}OCH_3$), 148.1 ($\underline{C}OCH_3$), 147.3 ($\underline{C}OCH_3$), 146.1 ($\underline{C}OCH_3$), 115.8 (C-1), 109.1 (C-6), 62.8 (OCH_3), 61.6 (OCH_3), 61.4 (OCH_3), 56.4 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2934, 2853, 1694, 1672, 1595, 1463, 1400, 1337, 1284, 1234, 1126, 1071, 1024, 998, 922, 861, 716.

HRMS (ESI): *m*/*z* = $[M]^{\bullet-}$ calcd for $C_{11}H_{13}O_6^{\bullet-}$: 241.0712; found 241.0718.

Literature known compound.[217]

Ethyl 3-oxo-3-(2,3,4,5-tetramethoxyphenyl)propanoate (318)



$C_{15}H_{20}O_7$

M = 312.3180 g/mol

This compound was prepared from

a) aldehyde **354** (8.62 g, 38.1 mmol), $SnCl_2$ (1.77 g, 9.33 mmol) and ethyl diazoacetate (15% in toluene, 37.7 mL, 49.5 mmol) in accordance with **General procedure R1**. Purification by FCC afforded product **309** as an amber colored oil of inseparable of keto-enol tautomers (3.11 g, 9.96 mmol, 26%).
b) carboxylic acid **317** (9.23 g, 38.1 mmol), $SOCl_2$ (27.8 mL, 381 mol), ethyl potassium malonate (8.52 g, 49.5 mmol), $MgCl_2$ (6.23 g, 64.8 mmol) and NEt_3 (18.6 mL, 133 mmol) in accordance with **General procedure R2**. Purification by FCC afforded product **318** as an amber colored oil of inseparable of keto-enol tautomers (6.40 g, 20.5 mmol, 54%).

<u>β-Ketoester:</u>

R_f: 0.36 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.16 (s, 1H, 6-H), 4.21 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 3.97 (s, 5H, $COCH_2CO$ and OCH_3), 3.92 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 1.27 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 192.3 ($\underline{C}OCH_2CO$), 168.3 ($COCH_2\underline{C}O$), 149.4 (OCH_3), 149.2 (OCH_3), 148.3 (OCH_3), 146.8 (OCH_3), 124.9 (1-C), 107.1 (C-6), 61.5 ($CO\underline{C}H_2CO$ or OCH_3), 61.4 ($CO\underline{C}H_2CO$ or OCH_3), 61.3 ($CO\underline{C}H_2CO$ or OCH_3), 61.2 ($CO\underline{C}H_2CO$ or OCH_3), 56.3 (OCH_3), 50.0 ($CO\underline{C}H_2CO$), 14.3 ($OCH_2\underline{C}H_3$).

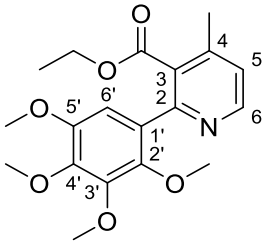
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2924, 1737, 1671, 1590, 1487, 1464, 1407, 1346, 1195, 1134, 1096, 1057, 999, 954, 806.

HRMS (ESI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{20}O_7^{\bullet+}$: 312.1209; found 312.1195.

<u>Enol:</u>

^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 12.74 (s, 0.10H, OH), 6.00 (s, 0.11H, vinyl-H), 1.34 (t, J = 7.1 Hz, 0.41H, $OCH_2C\underline{H}_3$).

Ethyl 2-(2,3,4,5-tetramethoxyphenyl)-4-methylnicotinate (319)



$C_{19}H_{23}NO_6$

M = 361.3940 g/mol

This compound was prepared in accordance with **General procedure E** from β-ketoester **318** (6.40 g, 20.5 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 2.05 mL, 4.51 mmol), crotonaldehyde (2.38 mL, 28.7 mmol) and hydroxylammonium chloride (4.70 g, 67.6 mmol). Purification by FCC afforded the product **319** as a yellow oil (1.78 g, 4.93 mmol, 24%)

R_f: 0.30 (hexanes/EtOAc 3:2).

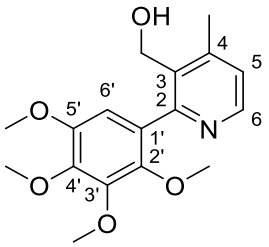
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.6 (d, J = 5.06 Hz, 1H, 6-H), 7.2 (dd, J = 5.02, 0.81 Hz, 1H, 5-H), 6.7 (s, 1H, 6'-H), 4.1 (q, J = 7.15 Hz, 2H, $OC\underline{H}_2CH_3$), 3.9 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 3.8 (s, 3H, OCH_3), 3.6 (s, 3H, OCH_3), 2.5 (d, J = 0.73 Hz, 3H, CH_3), 1.0 (t, J = 7.13 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 167.8 (COO), 155.0 (C-2), 149.8 (C-6), 149.4 ($\underline{C}OCH_3$), 147.1 ($\underline{C}OCH_3$), 146.2 (C-4), 145.3 ($\underline{C}OCH_3$), 143.5 ($\underline{C}OCH_3$), 130.0 (C-3), 129.1 (C-1'), 124.3 (C-5), 108.1 (C-6'), 61.5 (OCH_3), 61.4 (OCH_3), 61.4 (OCH_3), 61.2 ($O\underline{C}H_2CH_3$), 56.3 (OCH_3), 20.1 (CH_3), 13.9 ($OCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2935, 1721, 1573, 1491, 1463, 1401, 1240, 1116, 1064, 1005.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{19}H_{23}NO_6^{\bullet+}$: 361.1525; found 361.1528.

(4-Methyl-2-(2,3,4,5-tetramethoxyphenyl)pyridin-3-yl)methanol (320)



$C_{17}H_{21}NO_5$

M = 319.3570 g/mol

This compound was prepared in accordance with **General procedure Q** from ester **319** (1.02 g, 2.83 mmol) and LAH (322 mg, 8.49 mmol). Purification by FCC afforded the product **320** as a white solid (600 mg, 1.88 mmol, 66%).

R_f: 0.23 (hexanes/EtOAc 2:1 + 1% NEt_3).

M.p.: 106 – 107 °C.

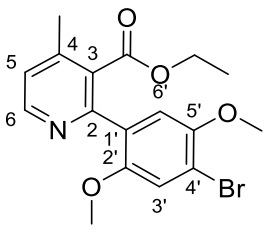
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.48 (d, J = 4.96 Hz, 1H, 6-H), 7.18 (d, J = 4.95 Hz, 1H, 5-H), 6.63 (s, 1H, 6‘-H), 4.57 – 4.48 (m, 1H, C$\underline{H}_2$OH), 4.39 – 4.31 (m, 1H, C$\underline{H}_2$OH), 3.99 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.40 (dd, J = 10.84, 2.69 Hz, 1H, $CH_2O\underline{H}$), 2.55 (d, J = 0.64 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 155.3 (C-2), 150.4 ($\underline{C}OCH_3$), 148.7 (C-6), 148.2 (C-4), 146.8 ($\underline{C}OCH_3$), 144.2 ($\underline{C}OCH_3$), 143.0 ($\underline{C}OCH_3$), 133.7 (C-3), 129.5 (C-1’), 125.1 (C-5´), 108.0 (C-6’), 62.0 (OCH_3), 61.6 (OCH_3), 61.2 (OCH_3), 60.7 (C$\underline{H}_2$OH), 56.1 (OCH_3), 18.9 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3175, 2936, 1586, 1492, 1455, 1414, 1399, 1118, 1074, 1004, 832.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{17}H_{21}NO_5^{\bullet+}$: 319.1420; found 319.1415.

Ethyl 2-(4-bromo-2,5-dimethoxyphenyl)-4-methylnicotinate (323)



$C_{17}H_{18}BrNO_4$

M = 380.2380 g/mol

This compound was prepared in accordance with **General procedure R1** from 4-bromo-2,5-dimethoxybenzaldehyde (**321**, 25.0 g, 100 mmol), ethyl diazoacetate (91.1 mL, 130 mmol) and $SnCl_2$ (4.74 g, 25.0 mmol). After attempt at purification by FCC, the resulting crude β-ketoester **322** (28.1 g, 85.0 mmol) was reacted with benzyltrimethylammonium hydroxide (40% in methanol, 8.50 mL, 18.7 mmol), crotonaldehyde (10.6 mL, 128 mmol) and hydroxylammonium chloride (19.5 g, 281 mmol) in accordance with **General procedure E**. Purification by FCC afforded the product **323** as an amber-colored solid (6.14 g, 16.1 mmol, 16% over two steps).

R_f: 0.07 (hexanes/EtOAc 8:1).

M.p.: 72 – 74 °C.

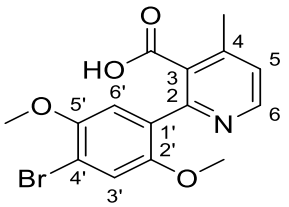
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.58 (d, J = 5.1 Hz, 1H, 6-H), 7.17 (dd, J = 5.1, 0.7 Hz, 1H, 5-H), 7.11 (s, 1H, 3'-H), 7.02 (s, 1H, 6'-H), 4.10 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 3.88 (s, 3H, 5'-OCH_3), 3.69 (s, 3H, 2'-OCH_3), 2.48 (d, J = 0.7 Hz, 3H, CH_3), 1.05 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 167.6 (COO), 154.4 (C-2), 150.8 (C-2'), 150.3 (C-5'), 150.0 (C-6), 146.4 (C-4), 129.9 (C-3), 129.5 (C-1'), 124.6 (C-5), 116.2 (C-3'), 114.7 (C-6'), 112.0 (C-4'), 61.2 ($O\underline{C}H_2CH_3$), 57.0 (5'-OCH_3), 56.2 (2'-OCH_3), 20.3 (CH_3), 13.9 ($OCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2974, 1719, 1492, 1279, 1209, 1136, 1029.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{13}{}^{79}BrNO_4{}^{\bullet+}$: 271.0845; found 271.0834.

2-(4-Bromo-2,5-dimethoxyphenyl)-4-methylnicotinic acid (324)



$C_{15}H_{14}BrNO_4$

M = 352.1840 g/mol

This compound was prepared in accordance with **General procedure D** from ester **323** (6.08 g, 16.0 mmol) and KOH (4.49 g, 80.0 mmol). Purification by FCC afforded the product **324** as a white solid (3.70 g, 10.5 mmol, 66%).

R_f: 0.25 (EtOAc + 1% AcOH).

M.p.: 236 – 237 °C.

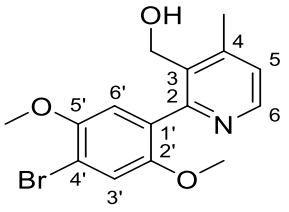
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 12.97 (s, 1H, COOH), 8.54 (d, J = 5.0 Hz, 1H, 6-H), 7.32 (dd, J = 5.0, 0.8 Hz, 1H, 5-H), 7.27 (s, 1H, 3'-H), 7.02 (s, 1H, 6'-H), 3.78 (s, 3H, 5'-OCH_3), 3.64 (s, 3H, 2'-OCH_3), 2.40 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 168.4 (COOH), 153.0 (C-2), 150.7 (C-2'), 149.3 (C-5'), 149.2 (C-6), 144.6 (C-4), 130.8 (C-3), 129.4 (C-1'), 124.4 (C-5), 116.0 (C-3'), 114.8 (C-6'), 110.8 (C-4'), 56.6 (5'-OCH_3), 55.8 (2'-OCH_3), 19.6 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3397, 1609, 1581, 1496, 1381, 1217, 1027, 838.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{14}{}^{79}BrNO_4{}^{\bullet+}$: 351.0106; found 351.0101.

(2-(4-Bromo-2,5-dimethoxyphenyl)-4-methylpyridin-3-yl)methanol (325)



$C_{15}H_{16}BrNO_3$

M = 338.2010 g/mol

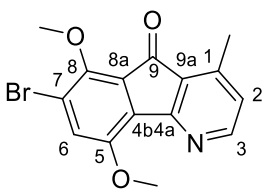
This compound was prepared in accordance with **General procedure S** from carboxylic acid **324** (1.06 g, 3.00 mmol) and dimethyl sulfide borane (2.0 M solution in THF, 1.80 mL, 3.60 mmol). Attempt at purification by FCC afforded the crude product **325** as a white resin (213 mg, 0.630 mmol, 21% crude yield).

R_f: 0.33 (hexanes/EtOAc 1:1).

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 8.73 (d, J = 6.0 Hz, 1H), 7.35 (d, J = 6.0 Hz, 1H), 7.30 (s, 1H), 6.77 (s, 1H), 4.45 – 4.31 (m, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 2.62 (s, 3H).

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{16}{}^{79}BrNO_3{}^{\bullet+}$: 337.0314; found 337.0312.

7-Bromo-5,8-dimethoxyonychine (326)



$C_{15}H_{12}BrNO_3$

M = 334.1690 g/mol

This compound was prepared from

a) crude pyridinemethanol **325** (84.5 mg, 0.250 mmol) and TBHP (5.5 M in decane, 0.121 mL, 1.00 mmol) in accordance with **General procedure A2**. Purification by FCC afforded the product **326** as a yellow solid (5.00 mg, 0.0150 mmol, 6%).
b) azafluorenone **180** (66.4 mg, 0.260 mmol) and NBS (60.8 mg, 0.338 mmol) in accordance with **General procedure F**. Purification by FCC afforded the product **326** as a yellow solid (79.0 mg, 0.236 mmol, 91%).

R_f: 0.34 (EtOAc).

M.p.: 179 – 180 °C.

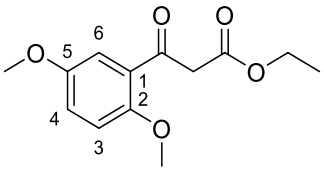
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.50 (d, J = 5.3 Hz, 1H, 3-H), 7.36 (s, 1H, 6-H), 6.94 (dd, J = 5.3, 0.8 Hz, 1H, 2-H), 4.03 (s, 3H, 5-OCH_3), 3.99 (s, 3H, 8-OCH_3), 2.62 (d, J = 0.7 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 190.5 (C-9), 164.4 (C-4a), 153.3 (C-3), 151.8 (C-5), 149.4 (C-8), 147.7 (C-1), 129.2 (C-4b), 127.0 (C-8a), 125.3 (C-2), 125.2 (C-9a), 123.8 (C-6), 122.1 (C-7), 62.2 (8-OCH_3), 57.1 (5-OCH_3), 17.5 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2924, 1707, 1599, 1556, 1475, 1422, 1290, 1235, 1183, 1071, 1027, 967.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{12}{}^{79}BrNO_3{}^{\bullet+}$: 333.0001; found 332.9996.

Ethyl 3-(2,5-dimethoxyphenyl)-3-oxopropanoate (328)



$C_{13}H_{16}O_5$

M = 252.2660 g/mol

This compound was prepared in accordance with **General procedure R2** from 2,5-dimethoxybenzoic acid (**327**, 20.0 g, 110 mmol), $SOCl_2$ (80.2 mL, 1.10 mol), ethyl potassium malonate (26.5 g, 154 mmol), $MgCl_2$ (18.0 g, 187 mmol) and NEt_3 (53.7 mL, 385 mmol).

Purification by FCC afforded product **328** as an amber colored oil of inseparable of keto-enol tautomers (19.4 g, 76.9 mmol, 70%).

β-Ketoester:

R_f: 0.42 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.41 (d, J = 3.2 Hz, 1H, 6-H), 7.07 (dd, J = 9.0, 3.2 Hz, 1H, 4-H), 6.90 (d, J = 9.0 Hz, 1H, 3-H), 4.17 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.96 (s, 2H, $COCH_2CO$), 3.84 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 1.23 (t, J = 7.1 Hz, 3H, OCH_2CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 192.7 ($COCH_2CO$), 168.2 ($COCH_2CO$), 153.8 (C-2), 153.6 (C-5), 126.3 (C-1), 121.9 (C-4), 113.9 (C-6), 113.1 (C-3), 60.9 (OCH_2CH_3), 55.8 (5-OCH_3), 55.8 (2-OCH_3), 50.6 ($COCH_2CO$), 14.2 (OCH_2CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2942, 1734, 1670, 1494, 1464, 1412, 1325, 1261, 1217, 1018, 812, 740.

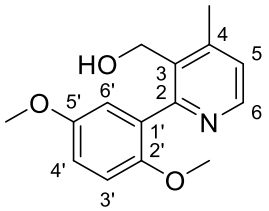
HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{13}H_{16}O_5^{\bullet+}$: 252.0998 found 252.0992.

Enol:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.71 (s, 0.07H, OH), 6.05 (s, 0.07H, vinyl-H), 4.25 (q, J = 7.1 Hz, 0.14H, OCH_2CH_3), 1.32 (t, J = 7.1 Hz, 0.23H, OCH_2CH_3).

Literature known compound.[289]

(2-(2,5-Dimethoxyphenyl)-4-methylpyridin-3-yl)methanol (329)



$C_{15}H_{17}NO_3$

M = 259.3050 g/mol

This compound was prepared in accordance with **General procedure Q** from ester **177** (2.39 g, 7.93 mmol) and LAH (903 mg, 23.8 mmol). Purification by FCC afforded the product **329** as a yellow solid (1.20 g, 4.62 mmol, 58%).

R_f: 0.33 (EtOAc).

M.p.: 123 – 124 °C.

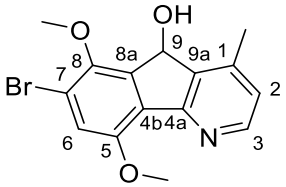
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 8.35 (d, J = 4.9 Hz, 1H, 6-H), 7.19 (dd, J = 4.9, 0.7 Hz, 1H, 5-H), 7.00 (d, J = 9.0 Hz, 1H, 3‘-H), 6.95 (dd, J = 9.0, 3.0 Hz, 1H, 4‘-H), 6.80 (d, J = 3.0 Hz, 1H, 6‘-H), 4.65 (t, J = 5.0 Hz, 1H, OH), 4.41 (dd, J = 11.9, 5.5 Hz, 1H, C$\underline{H}_2$OH), 4.18 (dd, J = 11.8, 4.2 Hz, 1H, C$\underline{H}_2$OH), 3.72 (s, 3H, 5‘-OCH_3), 3.61 (s, 3H, 2‘-OCH_3), 2.44 (d, J = 0.6 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 155.5 (C-2), 152.7 (C-5’), 150.5 (C-2’), 147.6 (C-6), 147.2 (C-4), 133.7 (C-1’), 130.4 (C-3), 124.7 (C-5), 116.5 (C-6’), 113.8 (C-3’), 112.1 (C-4’), 58.1 (CH_2OH), 55.8 (2’-OCH_3), 55.4 (5’-OCH_3), 18.7 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3195, 2841, 2359, 1586, 1496, 1456, 1268, 1213, 1048, 1017, 809, 724.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{17}NO_3^{\bullet+}$: 259.1208; found 259.1213.

7-Bromo-5,8-dimethoxy-4-azafluoren-9-ol (330)



$C_{15}H_{14}BrNO_3$

M = 336.1850 g/mol

$NaBH_4$ (11.3 mg, 0.300 mmol) was added to a solution of azafluorenone **326** (66.8 mg, 0.200 mmol) in methanol (10 mL) and stirred at room temperature for 1 h. Water (10 mL) was added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by FCC afforded the product **330** as a yellow solid (57.0 mg, 0.170 mmol, 85%).

R_f: 0.22 (EtOAc).

M.p.: 157 – 158 °C.

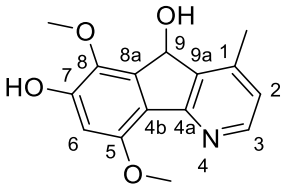
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.33 (d, J = 5.2 Hz, 1H, 3-H), 7.07 (s, 1H, 6-H), 6.82 (dd, J = 5.3, 0.8 Hz, 1H, 2-H), 5.76 (s, 1H, 9-H), 4.05 (s, 3H, 8-OCH_3), 3.95 (s, 3H, 5-OCH_3), 3.08 (bs, 1H, OH), 2.50 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 158.1 (C-4a), 152.1 (C-5), 150.2 (C-3), 148.4 (C-8), 144.9 (C-1), 140.2 (C-8a or C-9a), 136.6 (C-8a or C-9a), 127.5 (C-4b), 123.4 (C-2), 118.3 (C-7), 117.4 (C-6), 71.3 (C-9), 61.5 (8-OCH_3), 56.7 (5-OCH_3), 17.9 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3340, 2944, 1603, 1485, 1476, 1390, 1246, 1029, 830.

HRMS (EI): *m*/*z* = $[M-H]^{\bullet-}$ calcd for $C_{15}H_{13}{}^{79}BrNO_3{}^{\bullet-}$: 334.0077; found 334.0079.

5,8-Dimethoxy-7-hydroxy-1-methyl-4-azafluoren-9-ol (331)



$C_{15}H_{15}NO_4$

M = 273.2880 g/mol

To a solution of azafluorenone **101** (10.9 mg, 0.0400 mmol, 1.00 equiv.) in methanol (5.0 mL) $NaBH_4$ (10.6 mg, 0.280 mmol, 7.00 equiv.) was added and the mixture was stirred at room temperature for 2 h. The mixture was quenched with water, extracted with DCM/Isobutanol (1:1, 3 x 10 mL) and gave the crude product **331** as a yellow solid (10.0 mg, 0.0367 mmol, 91% crude yield). Due to the compound's high polarity, it could not be purified effectively.

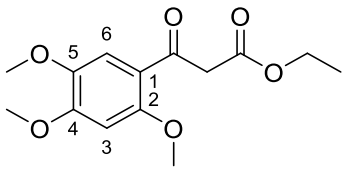
R_f: 0.12 (EtOAc + 1% NEt_3).

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 9.6 (s, 1H), 8.2 (d, *J* = 5.1 Hz, 1H), 6.9 (d, *J* = 5.1 Hz, 1H), 6.5 (s, 1H), 5.6 (d, *J* = 9.3 Hz, 1H), 5.5 (d, *J* = 9.3 Hz, 1H), 3.8 (s, 3H), 3.8 (s, 3H), 2.4 (s, 3H).

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{15}NO_4{}^{\bullet+}$: 273.1001; found 273.1003.

Literature known compound.[95]

Ethyl 2,4,5-trimethoxybenzoylacetate (333)



$C_{14}H_{18}O_6$

M = 282.2920 g/mol

This compound was prepared in accordance with **General procedure R2** from carboxylic acid **332** (21.2 g, 100 mmol), $SOCl_2$ (73.7 mL, 1.00 mol), and ethyl potassium malonate (25.8 g, 150 mmol), $MgCl_2$ (24.0 g, 250 mmol) and NEt_3 (30.7 mL, 220 mmol). Purification by FCC gave the product **333** as a white solid (18.8 g, 66.4 mmol, 66%).

R_f: 0.54 (hexanes/EtOAc 10:1).

M.p.: 65 – 66 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.50 (s, 1H, 6-H), 6.47 (s, 1H, 3-H), 4.18 (q, J = 7.1 Hz, 2H, $COOC\underline{H}_2CH_3$), 3.95 (s, 3H, OCH_3), 3.93 (s, 2H, $COCH_2COO$), 3.89 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 1.24 (t, J = 7.1 Hz, 3H, $COOCH_2C\underline{H}_3$).

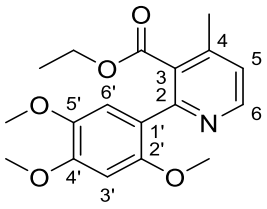
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.0 ($\underline{C}OCH_2COO$), 168.7 ($COCH_2\underline{C}OO$), 155.8 (C-2 or C-4), 154.9 (C-2 or C-4), 143.4 (C-5), 117.7 (C-1), 112.6 (C-6), 96.0 (C-3), 61.0 ($COO\underline{C}H_2CH_3$), 56.4 (OCH_3), 56.3 (OCH_3), 56.0 (OCH_3), 50.9 ($CO\underline{C}H_2COO$), 14.3 ($COOCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3004, 2944, 2837, 1723, 1654, 1605, 1512, 1469, 1401, 1353, 1324, 1272, 1192, 1130, 1020, 885, 823.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{14}H_{18}O_6^{\bullet+}$: 282.1103; found 282.1099.

Literature known compound.[290]

Ethyl 2-(2,4,5-trimethoxyphenyl)-4-methylnicotinate (334)



$C_{18}H_{21}NO_5$

M = 331.3680 g/mol

This compound was prepared in accordance with **General procedure E** from β-ketoester **333** (18.5 g, 65.5 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 2.05 mL, 4.51 mmol), crotonaldehyde (2.38 mL, 28.7 mmol) and hydroxylammonium chloride (4.70 g, 67.6 mmol) and gave the crude product as a black oil (4.47 g). Purification proved difficult as side product would co-elute so the product **334** containing remaining impurities after one FCC-run was used in the next step. For analytical purposes a small amount of pure product was isolated *via* preparative TLC.

R_f: 0.48 (EtOAC).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.57 (d, J = 5.1 Hz, 1H, 6-H), 7.11 (dd, J = 5.1, 0.7 Hz, 1H, 5-H), 7.00 (s, 1H, 6‘-H), 6.53 (s, 1H, 3‘-H), 4.11 (q, J = 7.1 Hz, 2H, $COOC\underline{H}_2CH_3$), 3.92 (s,

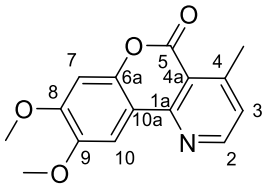
3H, 2'-OCH_3 or 4'-OCH_3), 3.86 (s, 3H, 5'-OCH_3), 3.70 (s, 3H, 2'-OCH_3 or 4'-OCH_3), 2.46 (d, *J* = 0.7 Hz, 3H, CH_3), 1.05 (t, *J* = 7.1 Hz, 3H, $COOCH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$): *δ* (ppm) = 168.0 (COO), 155.0 (C-2), 151.0 (C-2' or C-4'), 150.2 (C-2' or C-4'), 149.8 (C-6'), 146.0 (C-4), 143.3 (C-5'), 130.1 (C-3), 124.0 (C-5), 121.1 (C-1'), 114.2 (C-6'), 97.2 (C-3'), 61.0 ($COO\underline{C}H_2CH_3$), 56.5 (5'-OCH_3), 56.4 (2'-OCH_3 or 4'-OCH_3), 56.3 (2'-OCH_3 or 4'-OCH_3), 20.2 (CH_3), 13.9 ($COOCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2932, 1720, 1511, 1454, 1417, 1283, 1267, 1205, 1126, 1066, 1030, 727.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{18}H_{21}O_3N^{\bullet+}$: 331.1420; found 331.1417.

Polynemoraline C (335)



$C_{15}H_{13}NO_4$

M = 271.2720 g/mol

This compound was prepared in accordance with **General procedure C** from crude nicotinic acid ester **334** (250 mg) and PPA (2.50 g). Purification by FCC afforded the product (**335**) as white solid (8.00 mg, 0.0295 mmol, 4% over two steps).

R_f: 0.22 (hexanes/EtOAc 2:1).

M.p.: 257 – 259 °C (decomposition).

^{1}H NMR (500 MHz, $CDCl_3$): *δ* (ppm) = 8.75 (d, *J* = 4.9 Hz, 1H, 2H), 7.97 (s, 1H, 7-H), 7.23 (d, *J* = 4.8 Hz, 1H, 3-H), 6.85 (s, 1H, 10-H), 4.03 (s, 3H, 8-OCH_3), 3.97 (s, 3H, 9-OCH_3), 2.87 (s, 3H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): *δ* (ppm) = 161.1 (C-5), 154.3 (C-2), 153.8 (C-4), 153.3 (C-1a), 153.0 (C-9), 147.9 (C-6a), 146.8 (C-7), 125.9 (C-3), 115.5 (C-4a), 111.9 (C-10a), 105.5 (C-7), 99.9 (C-10), 56.5 (8-OCH_3), 56.5 (9-OCH_3), 23.1 (CH_3).

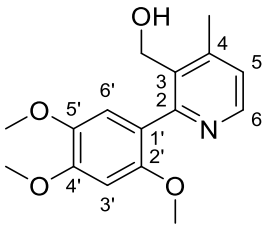
HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{13}NO_4^{\bullet+}$: 271.0845; found 271.0844.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1715, 1617, 1560, 1470, 1434, 1358, 1318, 1272, 1260, 1233, 1165, 1045, 1016, 991, 863, 830, 804, 782, 672.

HPLC purity (Method 2b): >95% (210 nm), >95% (254 nm).

Literature known compound.[291]

(4-Methyl-2-(2,4,5-trimethoxyphenyl)pyridin-3-yl)methanol (336)



$C_{16}H_{19}NO_4$

M = 289.3310 g/mol

This compound was prepared in accordance with **General procedure Q** from crude ester **334** (4.47 g) and LAH (2.05 g mg, 54.0 mmol). Purification by FCC afforded the product **336** as a white solid (1.62 g, 5.59 mmol, 9% over two steps).

R_f: 0.13 (EtOAc).

M.p.: 107 – 108 °C.

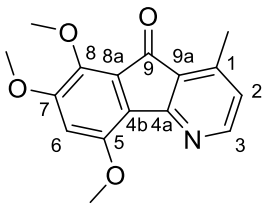
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) = 8.34 (d, J = 4.8 Hz, 1H, 6-H), 7.16 (dd, J = 4.8, 0.8 Hz, 1H, 5-H), 6.84 (s, 1H, 6'-H), 6.74 (s, 1H, 3'-H), 4.62 (s, 1H, OH), 4.41 (d, J = 11.7 Hz, 1H, CH_2), 4.23 (d, J = 11.7 Hz, 1H, CH_2), 3.85 (s, 3H, 2'-OCH_3 or 4'-OCH_3), 3.70 (s, 3H, 5'-OCH_3), 3.65 (s, 3H, 2'-OCH_3 or 4'-OCH_3), 2.44 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ (ppm) = 155.5 (C-2), 150.7 (C-2' or C-4'), 149.4 (C-2' or C-4'), 147.5 (C-6), 147.1 (C-4), 142.3 (C-5'), 134.0 (C-3), 124.4 (C-5), 120.8 (C-1'), 115.2 (C-6'), 97.9 (C-3'), 58.2 (CH_2), 56.2 (5'-OCH_3), 56.1 (2'-OCH_3 or 4'-OCH_3), 55.9 (2'-OCH_3 or 4'-OCH_3), 18.8 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3345, 1511, 1455, 1272, 1206, 1163, 1027, 838.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{16}H_{19}NO_4^{\bullet+}$: 289.1314; found 289.1308.

5,7,8-Trimethoxyonychine (337)



$C_{16}H_{15}NO_4$

M = 285.2990 g/mol

This compound was prepared in accordance with **General procedure A2** from pyridinemethanol **336** (545 mg, 1.60 mmol) and TBHP (5.5 M in decane, 1.16 mL, 6.40 mmol). Purification by FCC afforded the product **337** as an orange yellow solid (73.0 mg, 0.256 mmol, 16%).

R_f: 0.16 (EtOAc + 1% NEt_3).

M.p.: 166 – 167 °C.

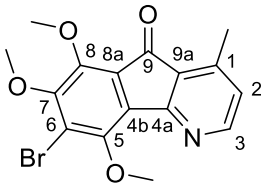
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.41 (d, J = 5.3 Hz, 1H, 3-H), 6.81 (dd, J = 5.4, 0.7 Hz, 1H, 2-H), 6.63 (s, 1H, 6-H), 4.02 (s, 3H, 5-OCH_3 or 7-OCH_3), 3.96 (s, 3H, 8-OCH_3), 3.93 (s, 3H, 5-OCH_3 or 7-OCH_3), 2.58 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.2 (C-9), 165.0 (C-4a), 156.9 (C-5 or C-7), 153.1 (C-3), 152.0 (C-5 or C-7), 147.3 (C-1), 142.7 (C-8), 127.3 (C-8a), 125.7 (C-9a), 124.0 (C-2), 120.2 (C-4b), 103.2 (C-6), 61.9 (8-OCH_3), 56.9 (5-OCH_3 or 7-OCH_3), 56.6 (5-OCH_3 or 7-OCH_3), 17.5 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1704, 1602, 1560, 1495, 1430, 1381, 1301, 1244, 1213, 1027, 966, 826.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{16}H_{15}NO_4^{\bullet+}$: 285.1001; found 285.0999.

6-Bromo-5,7,8-trimethoxyonychine (338)



$C_{16}H_{14}BrNO_4$

M = 364.1950 g/mol

This compound was prepared in accordance with **General procedure F** from azafluorenone **337** (52.2 mg, 0.183 mmol) and NBS (42.8 mg, 0.238 mmol). Purification by FCC afforded the product **338** as a yellow solid (43.0 mg, 0.118 mmol, 65%).

R_f: 0.38 (hexanes/EtOAc 4:1).

M.p.: 152 – 153 °C.

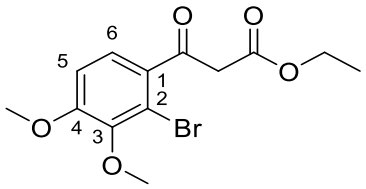
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.49 (d, J = 5.3 Hz, 1H, 3-H), 6.94 (dd, J = 5.3, 0.8 Hz, 1H, 2-H), 4.05 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 2.62 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 190.0 (C-9), 163.3 (C-4a), 154.2 (C-5 or C-7 or C-8), 153.2 (C-3), 149.4 (C-5 or C-7 or C-8), 149.2 (C-5 or C-7 or C-8), 147.5 (C-1), 130.0 (C-4b or C-8a), 126.2 (C-9a), 125.9 (C-4b or C-8a), 125.3 (C-2), 122.8 (C-6), 62.3 (OCH_3), 61.7 (OCH_3), 61.2 (OCH_3), 17.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2925, 2852, 1702, 1595, 1555, 1464, 1372, 1258, 1020, 825.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{16}H_{14}{}^{79}BrNO_4{}^{\bullet+}$: 363.0106; found 363.0125.

Ethyl 3-(2-bromo-3,4-dimethoxyphenyl)-3-oxopropanoate (339)



$C_{13}H_{15}BrO_5$

M = 331.1620 g/mol

This compound was prepared from

a) aldehyde **226** (24.5 g, 100 mmol), $SnCl_2$ (4.74 g, 25.0 mmol) and ethyl diazoacetate (15% in toluene, 102 mL, 120 mmol) in accordance with **General procedure R1**. Purification by FCC afforded product **339** as an amber colored oil of inseparable of keto-enol tautomers (12.5 g, 37.6 mmol, 38%).
b) 2-bromo-3,4-dimethoxybenzoic acid (**352**, 28.0 g, 100 mmol), $SOCl_2$ (72.9 mL, 1.00 mol), ethyl potassium malonate (22.4 g, 130 mmol), $MgCl_2$ (16.3 g, 170 mmol) and NEt_3 (48.8 mL, 350 mmol) in accordance with **General procedure R2**. Purification by FCC afforded product **328** as an amber colored oil of inseparable of keto-enol tautomers (11.9 g, 35.8 mmol, 36%).

<u>β-Ketoester</u>

R_f: 0.38 (hexanes/EtOAc 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.38 (d, J = 8.6 Hz, 1H, 6-H), 6.90 (d, J = 8.6 Hz, 1H, 5-H), 4.18 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.01 (s, 2H, $COCH_2CO$), 3.92 (s, 3H, 3-OCH_3), 3.85 (s, 3H, 4-OCH_3), 1.24 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 194.0 ($\underline{C}OCH_2CO$), 167.3 ($COCH_2\underline{C}O$), 156.4 (C-3), 147.1 (C-4), 132.9 (C-1), 126.5 (C-6), 116.6 (C-2), 110.8 (C-5), 61.6 ($O\underline{C}H_2CH_3$), 60.7 (4-OCH_3), 56.3 (3-OCH_3), 48.8 ($CO\underline{C}H_2CO$), 14.2 ($OCH_2\underline{C}H_3$).

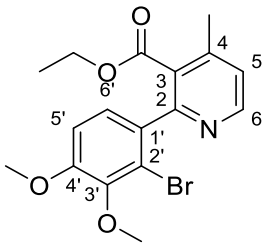
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2979, 2939, 1738, 1691, 1580, 1485, 1395, 1265, 1198, 1146, 1026, 997, 804.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{13}H_{15}{}^{79}BrO_5{}^{\bullet+}$: 330.0103; found 330.0103.

Enol:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.43 (s, 0.28H, OH), 5.43 (s, 0.27H, vinyl-H), 4.26 (q, *J* = 7.1 Hz, 1H, $OC\underline{H}_2CH_3$), 1.33 (t, *J*=7.1 Hz, 1H, $OCH_2C\underline{H}_3$).

Ethyl 2-(2-bromo-3,4-dimethoxyphenyl)-4-methylnicotinate (340)



$C_{17}H_{18}BrNO_4$

M = 380.2380 g/mol

This compound was prepared in accordance with **General procedure E** from β-ketoester **339** (18.4 g, 55.7 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 5.57 mL, 12.3 mmol), crotonaldehyde (6.92 mL, 83.6 mmol) and hydroxylammonium chloride (12.7 g, 184 mmol). Purification by FCC afforded the product **340** as an amber colored oil (6.57 g, 17.3 mmol, 31%).

R_f: 0.40 (hexanes/EtOAc 1:1).

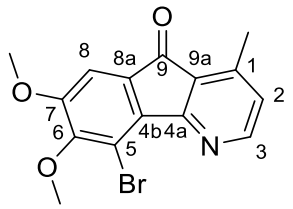
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.57 (d, *J* = 5.1 Hz, 1H, 6-H), 7.19 (dd, *J* = 5.1, 0.8 Hz, 1H, 5-H), 7.04 – 6.99 (m, 1H, 6‘-H), 6.89 (d, *J* = 8.4 Hz, 1H, 5‘-H), 4.06 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 3.90 (s, 3H, 4‘-OCH_3), 3.88 (s, 3H, 3‘-OCH_3), 2.46 (s, 3H, CH_3), 0.97 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 167.6 (COO), 156.7 (C-2), 153.7 (C-4’), 149.6 (C-6), 146.7 (C-3’), 146.1 (C-4), 134.4 (C-1’), 130.1 (C-3), 125.6 (C-6’), 124.6 (C-5), 118.6 (C-2’), 111.0 (C-5’), 61.3 ($O\underline{C}H_2CH_3$), 60.7 (3’-OCH_3), 56.3 (4’-OCH_3), 19.9 (CH_3), 13.8 ($OCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2976, 2935, 1720, 1592, 1578, 1490, 1446, 1289, 1259, 1119, 1066, 1029, 805.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{17}H_{18}{}^{79}BrNO_4{}^{\bullet+}$: 379.0419; found 379.0406.

5-Bromo-6,7-dimethoxyonychine (341)



$C_{15}H_{12}BrNO_3$

M = 334.1690 g/mol

This compound was prepared in accordance with **General procedure C** from ester **340** (1.10 g, 2.90 mmol) and PPA (3.00 g). Purification by FCC afforded the product **341** as a yellow solid (100 mg, 0.299 mmol, 10%).

R_f: 0.49 (hexanes/EtOAc 4:1).

M.p.: 190 – 191 °C.

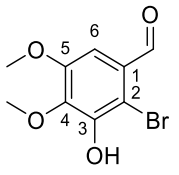
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.49 (d, *J* = 5.4 Hz, 1H, 3-H), 7.25 (s, 1H, 8-H), 6.92 (dd, *J* = 5.3, 0.7 Hz, 1H, 2-H), 3.96 (s, 3H, 7-OCH_3), 3.94 (s, 3H, 6-OCH_3), 2.61 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.6 (C-9), 165.4 (C-4a), 155.4 (C-7), 152.4 (C-3), 152.1 (C-6), 147.3 (C-1), 134.6 (C-4b), 132.6 (C-8a), 126.3 (C-9a), 125.2 (C-2), 113.6 (C-5), 107.0 (C-8), 61.0 (6-OCH_3), 56.6 (7-OCH_3), 17.5 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2924, 1707, 1574, 1458, 1353, 1290, 1263, 1095, 1051, 1025, 985, 916, 860, 796.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{15}H_{12}{}^{79}BrNO_3{}^{\bullet+}$: 333.0001; found 332.9989.

2-Bromo-3-hydroxy-4,5-dimethoxybenzaldehyde (343)



$C_9H_9BrO_4$

M = 261.0710 g/mol

This compound was prepared in accordance with **General procedure N** from 3,4-dimethoxy-5-hydroxybenzaldehyde (**342**, 4.77 g, 26.2 mmol) and NBS (4.90 g, 27.5 mmol), using THF (0.20 L) as the solvent to afford the product **343** as an off-white solid (6.75 g, 26.2 mmol, 99%).

R_f: 0.19 (hexanes/EtOAc 8:1).

M.p.: 145 – 146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.29 (s, 1H, CHO), 7.16 (s, 1H, 6-H), 6.25 (d, J = 0.8 Hz, 1H, OH), 4.02 (s, 3H, 4-OCH_3), 3.91 (s, 3H, 3-OCH_3).

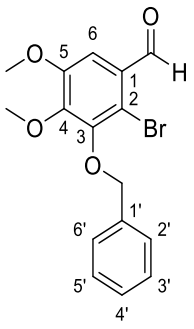
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.1 (CHO), 151.6 (C-5), 147.0 (C-3), 141.0 (C-4), 128.7 (C-1), 106.8 (C-2), 104.7 (C-6), 61.5 (4-OCH_3), 56.3 (3-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3373, 1680, 1574, 1428, 1330, 1259, 1199, 1143, 1114, 1014, 990, 839, 727, 655.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_9H_9{}^{79}BrO_4{}^{\bullet+}$: 259.9684; found: 259.9675.

Literature known compound.[222]

3-(Benzyloxy)-2-bromo-4,5-dimethoxybenzaldehyde (344)



$C_{16}H_{15}BrO_4$

M = 351.1960 g/mol

This compound was prepared in accordance with **General procedure L** from phenol **343** (6.74 g, 25.8 mmol), benzyl bromide (3.69 mL, 31.0 mmol) and K_2CO_3 (5.17 g, 51.7 mmol). Purification by FCC afforded the product **344** as a white solid (7.97 g, 22.7 mmol, 87%)

R_f: 0.35 (hexanes/EtOAc 8:1).

M.p.: 110 – 111 °C.

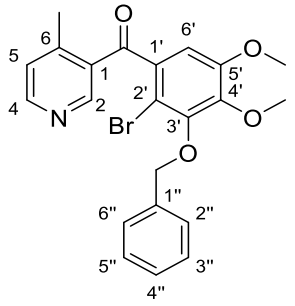
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.31 (s, 1H, COH), 7.58 – 7.54 (m, 2H, 2'-H and 6'-H), 7.44 – 7.36 (m, 3H, 3'-H and 4'-H and 5'-H), 7.33 (s, 1H, 6-H), 5.07 (s, 2H, OCH_2), 3.97 (s, 3H, 5-OCH_3), 3.93 (s, 3H, 4-OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.3 (CO), 153.3 (C-5), 149.8 (C-3), 149.1 (C-4), 136.6 (C-1'), 129.1 (C-1), 128.7 (C-2' and C-6'), 128.7 (C-3' and C-5'), 128.6 (C-4'), 116.2 (C-2), 107.8 (C-6), 75.7 (OCH_2), 61.5 (4-OCH_3), 56.4 (5-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1687, 1574, 1563, 1480, 1471, 1427, 1387, 1371, 1328, 1286, 1199, 1166, 1108, 1028, 994, 946, 901, 858, 844, 748, 693.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{16}H_{15}{}^{79}BrO_4{}^{\bullet+}$; 350.0154; found: 350.0150.

(3-(Benzyloxy)-2-bromo-4,5-dimethoxyphenyl)(4-methylpyridin-3-yl)methanone (346)



$C_{22}H_{20}BrNO_4$

M = 442.3090 g/mol

To a solution of diisopropylamine (3.44 mL, 24.6 mmol, 2.10 equiv.) in THF (20 mL) *n*-butyllithium (2.5 M in hexanes, 5.15 mL, 11.7 mmol, 1.10 equiv.) was added at -78 °C. The mixture was allowed to warm to -40 °C and stirred for 45 min, after which the solution was again cooled to -78 °C and 3-bromo-4-picolin (**167**, 1.30 mL, 11.7 mmol, 1.00 equiv.) was added dropwise. After letting the mixture stir for 30 min, a solution of aldehyde **344** (4.11 g, 11.7 mmol, 1.00 equiv.) in dry THF (25 mL) was added dropwise and the resulting mixture was allowed to warm to room temperature and stirred for 16 h. After completion of the reaction, it was quenched with water and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (0.100 L), washed with water (3 x 50 mL) and brine (3 x 50 mL), dried with $MgSO_4$, and the solvent removed *in vacuo* to give crude alcohol **345** (1.42 g, 3.20 mmol) which was used in the next step without further purification. MnO_2 (2.78 g, 32.0 mmol, 10.0 equiv.) was added to a solution of crude alcohol **345** (1.42 g, 3.20 mmol, 1.00 equiv.) in toluene (50 mL) and was heated to reflux with a Dean Stark trap for 20 h. The mixture was filtered, and the

solvent removed *in vacuo*. The crude product was purified *via* FCC to give the product **346** as a yellow oil (728 mg, 1.66 mmol, 14% over two steps).

R_f: 0.22 (hexanes/EtOAc 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.57 (d, J = 5.1 Hz, 1H, 4-H), 8.47 (s, 1H, 2-H), 7.55 – 7.49 (m, 2H, 2''-H and 6''), 7.42 – 7.33 (m, 3H, 3''-H, 4''-H and 5''), 7.24 (dt, J = 5.1, 0.7 Hz, 1H, 5-H), 6.84 (s, 1H, 6'-H), 5.08 (s, 2H, OCH_2), 3.95 (s, 3H, 4'-OCH_3), 3.89 (s, 3H, 5'-OCH_3), 2.59 (s, 3H, CH_3).

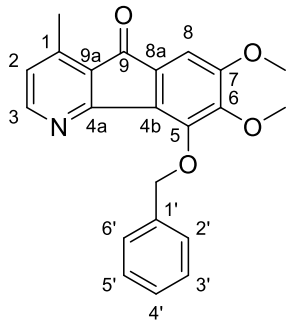
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 196.2 (CO), 153.3 (C-5'), 152.2 (C-4), 151.9 (C-2), 150.2 (C-3'), 149.0 (C-6), 145.8 (C-4'), 136.7 (C-1''), 136.2 (C-1'), 133.1 (C-1), 128.7 (C-2'' and 6''), 128.6 (C-3'' and 5''), 128.5 (C-4''), 126.8 (C-5), 109.0 (C-6'), 108.2 (C-2'), 75.6 (OCH_2), 61.5 (4'-OCH_3), 56.5 (5'-OCH_3), 20.9 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2938, 1667, 1588, 1478, 1405, 1366, 1330, 1214, 1105, 1002, 742, 697.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{22}H_{20}{}^{79}BrNO_4{}^{\bullet+}$: 441.0576; found: 441.0562.

The synthesis was performed using the method of Kraus and Kempema.[146]

5-Benzyloxy-6,7-dimethoxyonychine (347)



$C_{22}H_{19}NO_4$

M = 361.3970 g/mol

A solution of benzoylpyridine **346** (177 mg, 0.400 mmol, 1.00 equiv.), *tert*-butylammonium chloride (167 mg, 0.600 mmol, 1.50 equiv.), $Pd(OAc)_2$ (8.98 mg, 0.0400 mmol, 0.100 equiv., 10 mol%) and K_2CO_3 (60.1 mg, 0.600 mmol, 1.50 equiv.) in DMF (10 mL) was stirred at 100 °C for 18 h. The solution was allowed to cool to room temperature and water (20 mL) was added. The mixture was extracted with EtOAc (3 x 20 mL), washed with water (3 x 20 mL) and brine (3 x.20 mL). The combined organic phases were dried over $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified *via* FCC to give the product **347** as a yellow solid (10.0 mg, 0.0277 mmol, 7%).

R_f: 0.70 (hexanes/EtOAc 2:1).

M.p.: 137 – 139 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.42 (d, J = 5.3 Hz, 1H, 3-H), 7.69 – 7.58 (m, 2H, 2'-H and 6'-H), 7.39 – 7.29 (m, 3H, 3'-H, 4'-H and 5'-H), 7.10 (s, 1H, 8-H), 6.85 (dd, J = 5.4, 0.7 Hz, 1H, 2-H), 5.30 (s, 2H, OCH_2), 3.93 (s, 6H, 6-OCH_3 and 7-OCH_3), 2.64 – 2.54 (s, 3H, CH_3).

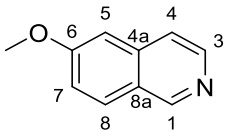
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 192.7 (C-9), 165.3 (C-4a), 155.8 (C-7), 152.9 (C-3), 148.9 (C-6), 148.7 (C-5), 146.8 (C-1), 137.3 (C-1'), 131.3 (C-8a), 129.1 (C-2' and C-6'), 128.9 (C-4b), 128.4 (C-3' and C-5'), 128.3 (C-4'), 126.1 (C-9a), 124.5 (C-2), 103.9 (C-8), 76.3 (OCH_2), 61.6 (6-OCH_3 or 7-OCH_3), 56.6 (6-OCH_3 or 7-OCH_3), 17.4 (CH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3061, 3028, 2919, 2848, 1708, 1596, 1557, 1462, 1425, 1364, 1244, 1193, 1148, 1121, 1081, 1030, 990, 978, 944, 902, 867, 852, 800, 786, 753, 737, 694.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{22}H_{19}NO_4^{\bullet+}$: 361.1314; found: 361.1303.

The synthesis was performed using the method of Kraus and Kempema.[146]

6-Methoxyisoquinoline (369)



$C_{10}H_9NO$

M = 159.1880 g/mol

Aminoacetaldehyde dimethyl acetal (12.0 mL, 100 mmol) was added to a solution of 4-methoxybenzaldehyde (**366**; 13.6 g, 100 mmol) in toluene (0.25 L). The mixture was heated to reflux for 16 h using a Dean-Stark trap. The solvent was then removed *in vacuo* and the crude product **367** dissolved in THF (0.25 L). Ethyl chloroformate (9.56 mL, 100 mmol) and triethylphosphite (20.6 mL, 120 mmol) were added successively at 0 °C. The mixture was allowed to warm to room temperature and stirred for an additional 16 h. The solvent was removed *in vacuo* and the crude product **368** dissolved in DCM (0.25 L) after which $TiCl_4$ (11.1 mL, 100 mmol) was added. The resulting solution was heated to reflux and stirred for 16 h after which the mixture was poured on ice. The aqueous layer was washed with DCM (3 x 0.10 L) and poured into a saturated aqueous solution of $KNaC_4H_4O_6 \cdot 4H_2O$ (0.30 L). The pH of the solution was adjusted to pH = 9 with concentrated aqueous ammonia and the mixture extracted with DCM several times. The combined organic phases were dried with $MgSO_4$, and the

solvent removed *in vacuo*. The crude product was purified *via* FCC to give the product **369** as a yellow oil (7.14 g, 44.9 mmol, 45% over three steps)

R_f: 0.36 (hexanes/EtOAc 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.10 (t, *J* = 0.9 Hz, 1H, 1-H), 8.44 (d, *J* = 5.8 Hz, 1H, 3-H), 7.85 (dt, *J* = 9.0, 0.6 Hz, 1H, 8-H), 7.53 (dt, *J* = 5.9, 1.0 Hz, 1H, 4-H), 7.22 (dd, *J* = 9.0, 2.4 Hz, 1H, 7-H), 7.05 (d, *J* = 2.5 Hz, 1H, 5-H), 3.94 (s, 3H, OCH_3).

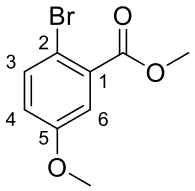
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 161.0 (C-6), 151.8 (C-1), 143.7 (C-3), 137.9 (C-4a), 129.5 (C-8), 124.7 (C-8a), 120.4 (C-7), 119.8 (C-4), 104.1 (C-5), 55.6 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3372, 1711, 1625, 1474, 1399, 1332, 1263, 1226, 1160, 1127, 1024, 954, 852, 820, 700, 661.

HRMS (EI): *m/z* = $[M]^{\bullet+}$ calcd for $C_{10}H_9NO^{\bullet+}$: 159.0684; found: 159.0709.

Literate known compound.[292] The synthesis was performed as described by Hendrickson and Rodriguez.[236a]

Methyl 2-brom-5-methoxybenzoate (371)



$C_9H_9BrO_3$

M = 245.0720 g/mol

To a solution carboxylic acid **285** (4.76 g, 31.0 mmol, 1.00 equiv) in MeOH (0.15 L) a catalytic amount of concentrated sulfuric acid was added. After the reaction was heated to reflux for 20 h, the solution was cooled to room temperature and water (0.10 L) was added. The solution was then neutralized with K_2CO_3 and extracted with EtOAc (3 x 0.10 L). The combined organic phases were washed with brine (3 x 50 mL), dried with $MgSO_4$ and the solvent evaporated *in vacuo*. The crude product **370** was afforded as a yellow oil (5.09 g) and used in the following step without further purification. Diphenyl disulfide (2.03 g, 9.18 mmol, 0.300 equiv.) was added to a solution of crude benzoate **370** (5.09 g, 30.6 mmol, 1.00 equiv.) in MeCN (0.20 L), after which NBS (16.5 g, 91.8 mmol, 3.00 equiv.) was added portionwise. The reaction was stirred at room temperature for 22 h before a mixture of saturated $NaHCO_3$ and $Na_2S_2O_3$ solutions (1:1, 0.20 L) was added. The resulting mixture was extracted with EtOAc (3 x 50 mL), the combined organic phases washed with brine (3 x 50 mL), dried over $MgSO_4$ and the solvent

evaporated *in vacuo*. The crude product was purified *via* FCC to give the product **371** as a colorless oil (5.80 g, 23.7 mmol, 76% over two steps).

R_f: 0.47 (hexanes/EtOAc 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.52 (d, J = 8.8 Hz, 1H, 3-H), 7.31 (d, J = 3.1 Hz, 1H, 6-H), 6.89 (dd, J = 8.8, 3.1 Hz, 1H, 4-H), 3.93 (s, 3H, $COOCH_3$), 3.81 (s, 3H, OCH_3).

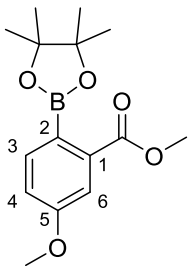
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 166.6 ($\underline{C}OOCH_3$), 158.7 (OCH_3), 135.2 (C-3), 132.9 (C-1), 119.2 (C-4), 116.4 (C-6), 112.1 (C-2), 55.8 (OCH_3), 52.7 ($COO\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2952, 1730, 1593, 1572, 1470, 1433, 1319, 1288, 1249, 1181, 1104, 1048, 1018, 815, 775.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_9H_9{}^{79}BrO_3{}^{\bullet+}$: 243.9735; found 243.9727.

Literature known compound.[293] The second step of the synthesis was performed as described by Hirose and coworkers.[294]

Methyl 5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (372)



$C_{15}H_{21}BO_5$

M = 292.1380 g/mol

Benzoate **371** (2.82 g, 11.5 mmol, 1.00 equiv.), bis(pinacolato)diborone (3.21 g, 12.7 mmol, 1.10 equiv.), KOAc (3.39 g, 34.5 mmol, 3.00 equiv.) and $Pd(dppf)Cl_2$ (421 mg, 0.575 mmol, 0.0500 equiv., 4 mol%) were dissolved in dry dioxane (50 mL) and stirred for 16 h at to 85 °C. The mixture was filtered through a bed of celite and the filtercake washed with EtOAc (3 x 50 mL). The organic phase was washed with water (3 x 30 mL), brine (3 x 30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC afforded the product **372** as a clear oil (2.40 g, 8.22 mmol, 71%).

R_f: 0.38 (hexanes/EtOAc 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.44 (d, J = 6.2 Hz, 1H, 3-H), 7.43 (s, 1H, 6-H), 7.04 (dd, J = 8.1, 2.6 Hz, 1H, 4-H), 3.90 (s, $COOCH_3$), 3.83 (s, 3H, 5-OCH_3), 1.39 (s, 12H, CH_3).

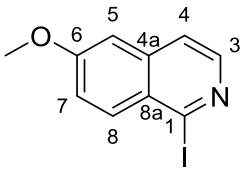
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 168.5 (COO), 160.5 (C-5), 135.8 (C-1 and C-2), 134.0 (C-3), 118.1 (C-4), 113.9 (C-6), 84.0 ($O_2\underline{C}_2(CH_3)_4$), 55.5 (5-$OCH_3$), 52.4 ($COO\underline{C}H_3$), 25.0 ($CH_3$).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2977, 1720, 1604, 1436, 1346, 1257, 1222, 1143, 1105, 1064, 1029, 962, 856, 790, 658.

HRMS (EI): m/z = $[M]^{\bullet+}$ calcd for $C_{15}H_{21}BO_5^{\bullet+}$: 292.1482; found 292.1477.

Literature known compound.[295] The synthesis for this compound was performed as described by Kraetzschmar et al.[295]

1-Iodo-6-methoxyisoquinoline (373)



$C_{10}H_8INO$

M = 285.0845 g/mol

TMPMg·LiCl (1.0 M in THF/toluene, 31.5 mL, 31.5 mmol, 1.50 equiv.) was added dropwise to a flame-dried Schlenk flask charged with a solution of isoquinoline **369** (3.34 g, 21.0 mmol, 1.00 equiv.) in dry THF (0.10 L) under nitrogen atmosphere. After stirring the solution for 4 h at room temperature, the solution was cooled to 0°C and a solution of iodine (8.00 g, 31.5 mmol, 1.50 equiv.) in dry THF (25 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 1 h, before it was quenched with saturated aqueous NH_4Cl solution (10 mL) and saturated $Na_2S_2O_3$ solution (10 mL). The mixture was then extracted with EtOAc (3 x 50 mL), and the combined organic phases were washed with brine (3 x 20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by FCC afforded the product **373** as a brown oil (2.84 g, 9.95 mmol, 47%).

R_f: 0.25 (hexanes/EtOAc 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.15 (d, J = 5.6 Hz, 1H, 3-H), 8.03 – 7.97 (m, 1H, 8-H), 7.46 (dd, J = 5.7, 0.9 Hz, 1H, 4-H), 7.27 (dd, J = 9.3, 2.5 Hz, 1H, 7-H), 6.99 (d, J = 2.5 Hz, 1H, 5-H), 3.96 (s, 3H, OCH_3).

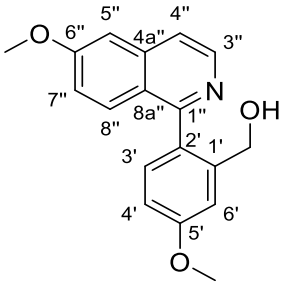
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 161.5 (C-6), 143.5 (C-3), 138.0 (C-4a), 134.8 (C-8), 127.6 (C-8a), 126.7 (C-1), 121.7 (C-7), 120.7 (C-4), 104.7 (C-5), 55.8 (OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3330, 2930, 2856, 1620, 1555, 1488, 1468, 1453, 1371, 1304, 1265, 1243, 1177, 1132, 1028, 960, 856, 745, 657.

HRMS (EI): *m*/*z* = $[M]^{\bullet+}$ calcd for $C_{10}H_8INO^{\bullet+}$: 284.9651; found 284.9644.

Literature known compound. The synthesis was performed as described by Melzer et al.[235]

(5-Methoxy-2-(6-methoxyisoquinolin-1-yl)phenyl)methanol (375)



$C_{18}H_{17}NO_3$

M = 295.3380 g/mol

This compound was prepared in accordance with **General procedure Q** from ester **182** (323 mg, 1.00 mmol) and LAH (152 mg, 4.00 mmol). Purification by FCC afforded the product **375** as a pale-yellow solid (271 mg, 0.916 mmol, 92%).

R_f: 0.20 (hexanes/EtOAc 1:1).

M.p.: 136 – 138°C.

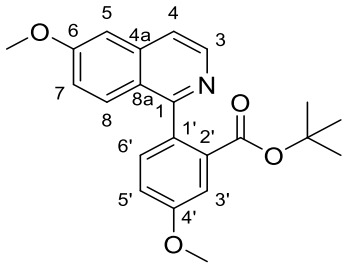
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.43 (d, *J* = 5.8 Hz, 1H, 3''-H), 7.91 (dt, *J* = 9.0, 0.8 Hz, 1H, 8''-H), 7.56 (dd, *J* = 5.8, 0.9 Hz, 1H, 4''-H), 7.39 (d, *J* = 8.5 Hz, 1H, 3'-H), 7.19 – 7.10 (m, 3H, 6'-H and 5''-H and 7''-H), 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H, 4'-H), 4.35 (s, 2H, CH_2), 3.97 (s, 6''-OCH_3), 3.91 (s, 3H, 5'-OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 161.1 (C-6''), 160.3 (C-5'), 159.7 (C-1''), 142.9 (C-1'), 141.5 (C-3''), 139.6 (C-4a''), 133.2 (C-3'), 131.0 (C-2'), 129.9 (C-8''), 123.2 (C-8a''), 120.3 (C-7''), 119.6 (C-4''), 116.1 (C-6'), 112.9 (C-4'), 104.7 (C-5''), 64.8 (CH_2), 55.7 (6''-OCH_3), 55.6 (5'-OCH_3).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2929, 1619, 1555, 1486, 1432, 1372, 1301, 1261, 1241, 1173, 1132, 1029, 958, 856, 811, 695.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}NO_3$ $[M]^{\bullet+}$; 295.1208; found 295.1205.

tert-Butyl 5-methoxy-2-(6-methoxyisoquinolin-1-yl)benzoate (376)



$C_{22}H_{23}NO_4$

M = 365.4290 g/mol

This compound was prepared in accordance with **General procedure A2** from alcohol **375** (90.1 mg, 0.305 mmol) and TBHP (5.5 M in decane, 0.139 mL) and tetra-*n*-butylammonium iodide (11.3 mg, 0.0305 mmol). Purification by FCC afforded an inseparable mixture of product **376** and an unidentified side-product as an off-white solid (9.00 mg, 0.0246 mmol, 8% crude yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.47 (d, *J* = 5.7 Hz, 1H), 7.59 – 7.51 (m, 4H), 7.37 (d, *J* = 8.4 Hz, 1H,), 7.17 – 7.12 (m, 1H), 7.12 – 7.05 (m, 3H), 3.95 (s, 3H), 3.92 (d, *J* = 0.8 Hz, 4H), 0.86 (s, 9H).

HRMS (ESI): *m*/*z* = $[M+H]^+$ calcd for $C_{22}H_{24}NO_4^+$: 366.1705; found 366.1706.

7 Appendices

7.1 Abbreviations

1,2-DCE	1,2-dichloroethane
Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
ASAP	atmospheric solids analysis probe
aq.	aqueous
Ar	aryl
BHT	butylated hydroxytoluene
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
calcd	calculated
conc.	Concentrated
CMS	compact mass spectrometer
d	doublet
DCFH-DA	dichlorodihydrofluorescein diacetate
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCM	dichloromethane
DIEA	diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dppf	1,1′-bis(diphenylphosphino)ferrocene
DPPH	(2,2-diphenyl-1-picrylhydrazyl)
EC_{50}	half maximal effective concentration

ED_{50}	median effective dose
EDA	ethyl diazoacetate
EI	electron ionisation
equiv.	equivalent
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
FCC	flash column chromatography
GAG	glycosaminoglycans
GC-MS	gas chromatography–mass spectrometry
HFIP	hexafluoroisopropanol
HIV	human immunodeficiency virus
HMO method	Hückel molecular orbital method
HMPC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
I	Kováts retention index
IC_{50}	half maximal inhibitory concentration
IFN	interferone
Ile	isoleucine
IR	infrared spectroscopy
IUPAC	International Union of Pure and AppliedChemistry
^{i}Pr	isopropyl
K_i	inhibition constant
LC-MS	liquid chromatography-mass spectrometry
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
L-NMMA	L-NG-monomethylarginine, acetate salt
LORA	low-oxygen-recovery assay
LPS	lipopolysaccharide
M	molecular weight
m	meta
MABA	microplate alamar blue assay
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MEM	methoxyethoxymethyl

MERS-CoV	middle east respiratory syndrome coronavirus
MIC	minimum inhibitory concentration
MOM	methoxymethyl
m.p.	melting point
MRP1	multidrug resistance protein 1
MRSA	methicillin-resistant *Staphylococcus aureus*
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
m/z	mass-to-charge ratio
NAD	nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NIST	national Institute of Standards and Technology
NMR	nuclear magnetic resonance
o	ortho
OLED	organic light-emitting device
ORAC	oxygen radical absorbance capacity
p	para
PAH	polycyclic aromatic hydrocarbons
PBP2a	penicillin binding protein 2a
PDE	phosphodiesterase
Ph	phenyl
pin	pinacol
pK_a	acid dissociation constant
PPA	polyphosphoric acid
PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
q	quartet
R_f	retardation factor
ROS	reactive oxygen species
RRT	relative retention time
rt	room temperature
SARS-CoV-2	severe acute respiratory syndrome coronavirus type 2
SEM	trimethylsilylethoxymethyl
t	triplet
t	tertiary
*t*Bu	*tert*-butyl
TBAC	tetra-*n*-butylammonium chloride

TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflyl
TFA	trifluoroacetic
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin-layer chromatography
TLC-MS	thin-layer chromatography-mass chromatography
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidino
tRi	total retention time of the substance
tRz	total retention time of the n-alkane
UV	ultraviolet
$\tilde{\nu}$	wavenumber

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