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Functionalized Phenanthridine and Dibenzopyranone Derivatives through Benzyne Cyclization – Application to the Total Syntheses of Trisphaeridine and *N*-Methylcrinasiadine

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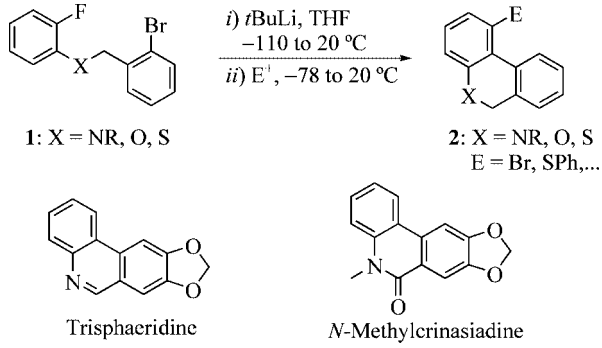
A series of regioselectively functionalized benzo[*c*]chromen-6-ones, phenanthridinones, and phenanthridine derivatives have been prepared by an anionic cyclization and in situ oxidation sequence starting from 2-bromobenzyl-2-fluorophenyl ethers and amines. These processes involve the generation of a benzyne-tethered aryllithium intermediate and subsequent 6-*exo*-*dig* cyclization. By applying this methodology to the appropriate starting materials, short and efficient syntheses of *Amaryllidaceae* alkaloids trisphaeridine and *N*-methylcrinasiadine have been achieved in good overall yields.

Introduction

Benzynes are highly electrophilic intermediates which have been widely used as versatile intermediates in organic synthesis.[1,2] The intramolecular addition of an aryne-tethered nucleophile, a process often called benzyne cyclization,[3] is a well-developed strategy for the creation of benzo-fused carbocycles and heterocycles.[4] This strategy has been successfully applied to the synthesis of a variety of heterocyclic compounds such as benzoxazole,[5] benzothiazole,[6] indoline,[7] isoindolinone,[8] and chromene[9] derivatives. In the vast majority of the reported examples, the nucleophile is a stabilized carbanion,[10] or a nitrogen, oxygen, or sulfur anion. However, the formation and cyclization of benzyne-tethered organolithiums remains a largely unexplored area and only a few examples with alkyllithiums have been reported.[11]

In this field, we have reported the intramolecular 5-*exo* anionic cyclization of benzyne-tethered vinyl and aryllithiums and its application to the synthesis of regioselectively functionalized indole, carbazole, dibenzofuran, and dibenzothiophene derivatives.[12] We have also demonstrated the possibility of carrying out 6-*exo* cyclizations in a process that allows the efficient preparation of dihydrophenanthridine, dibenzopyran, and dibenzothiopyran derivatives **2** in good yields (Scheme 1).[12b]



Scheme 1.

The phenanthrene-type skeleton is present in many natural products either in the carbocyclic or heterocyclic form. The *Amaryllidaceae* alkaloids are a group of natural products having in most cases a phenanthridine-type structure.[13] Two examples of this group of alkaloids that have been isolated from a few plants of *Amaryllidaceae* are trisphaeridine[14] and *N*-methylcrinasiadine[15] (Scheme 1). These and other phenanthridine and phenanthridinone alkaloids have been previously synthesized by several methods including palladium-catalyzed couplings and further cyclizations,[16] radical cyclizations,[17] or benzyne-mediated condensations,[18] among other synthetic methods.[19] These processes, however, generally lack the flexibility that would make them suitable for the regioselective introduction of

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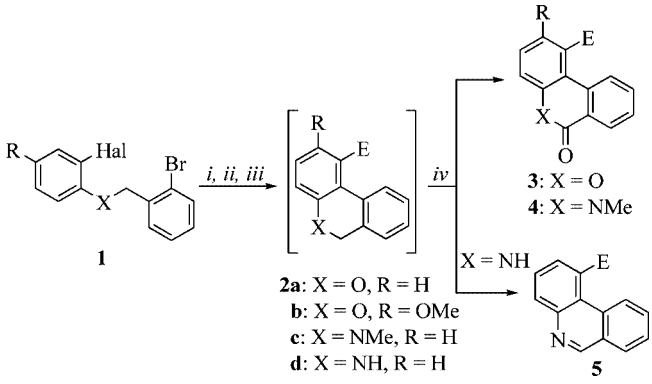
functional groups in the same step in which the cyclization process takes place.

Substituted 6*H*-dibenzo[*b*,*d*]pyran-6-ones are widespread in nature and exhibit biological activities.[20] In addition, these compounds have been used as intermediates in the synthesis of cannabinoids and various pharmaceutically interesting compounds with potential application as progesterone receptor agonists.[21] Among the various strategies developed for the synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-ones,[22] most of them rely on intramolecular palladium-catalyzed arylation reactions,[23] copper-catalyzed condensation of 2-bromobenzoic acids with phenols (Hurtley reaction),[24] dienone-phenol rearrangements,[25] or intramolecular radical cyclizations.[26] However, with the use of these methodologies it is not possible to introduce functional groups in the cyclization step and highly functionalized starting materials, not always easily available, are generally needed to generate regioselectively substituted heterocycles.

Firmly convinced by the potential of the anionic cyclization of benzyne-tethered aryllithiums as a useful methodology for the synthesis of functionalized heterocycles, we initiated a project directed at the search of a protocol for the in situ oxidation of dibenzo-fused six-membered heterocycles **2**. Thus, in this paper we report that regioselectively functionalized phenanthridine and dibenzopyranone derivatives could be efficiently accessed by anionic cyclization of benzyne intermediates and further functionalization and benzylic oxidation. Also, this strategy has been applied to the short and efficient syntheses of *Amaryllidaceae* alkaloids trisphaeridine and *N*-methylcrinasiadine.

Results and Discussion

Our studies started with the model reaction of 2-bromobenzyl-2-halophenyl ethers **1a**,**b**, which under treatment with 3.3 equiv. of *t*BuLi in THF from –110 to 20 °C, and further reaction with different electrophiles, afforded corresponding dibenzopyrans **2a**,**b**.[12b] Without purification, we found that 6*H*-benzo[*c*]chromenes **2a**,**b** were efficiently oxidized to corresponding 6*H*-benzo[*c*]chromen-6-ones **3** with the use of PCC as an oxidant in CH_2Cl_2 heated at reflux.[26b] Moreover, we have observed that the benzylic methylene in the chromene derivatives was selectively oxidized over the benzylic methylene in uncyclized byproducts, which allows easy separation and purification of desired dibenzopyranones **3**. In this way, regioselectively functionalized dibenzopyranones **3a**–**e** have been synthesized in moderate-to-good yields starting from ethers **1a**,**b** (Scheme 2; Table 1, Entries 1–5). For the synthesis of dibenzopyranone **3d**, an additional equivalent of PCC was needed because of the oxidation of the initially introduced hydroxy(*p*-tolyl)methyl group to the corresponding ketone.



Scheme 2. Synthesis of dibenzo[*b*,*d*]pyran-6-ones **3**, phenanthridinones **4**, and phenanthridines **5**; reagents and conditions: *i*) *t*BuLi (3.3 equiv. for **1a**,**b**, 3.5 equiv. for **1c**,**d**), THF, –110 to 20 °C; *ii*) E^+ (1.5 equiv.), –78 to 20 °C; *iii*) for **1d**, DIBAL-H (1.5 equiv.), [$NiCl_2$(dppp)] (4 mol-%), toluene, 20 °C; *iv*) PCC (3 equiv. for **2a**–**c**, 1 equiv. for **2d**), CH_2Cl_2, reflux.

When we applied this strategy to *N*-(2-bromobenzyl)-2-fluoro-*N*-methylaniline (**1c**), 5*H*-phenanthridin-6-ones **4** were isolated after benzylic oxidation with PCC of dihydrophenanthridine intermediates **2c** (Scheme 2; Table 1, Entries 6 and 7). Finally, treatment of *N*-allyl-*N*-(2-bromobenzyl)-2-fluoroaniline (**1d**) under the same reaction conditions gave rise to 1-functionalized 5-allyl-5,6-dihydrophenanthridines. Without isolation, the allyl group was easily removed by treatment with DIBAL-H and catalytic [$NiCl_2$(dppp)] in toluene,[27] and crude dihydrophenanthridines **2d** were treated with PCC. In this case, no oxidation of the benzylic methylene was observed and 1-functionalized phenanthridines **5** were obtained instead of the *N*-unsubstituted phenanthridones (Scheme 2; Table 1, Entries 8 and 9). We attributed this unexpected result to the absence of substituents on the nitrogen atom in dihydrophenanthridines **2d**, compared with **2c**, which could favor the observed dehydrogenation

Table 1. Synthesis of dibenzo[*b*,*d*]pyran-6-ones **3**, phenanthridinones **4**, and phenanthridines **5**.

Entry	Starting product	X	Halogen	R	E^+	Product	E	Yield [%][a]
1	**1a**	O	F	H	MeOH	**3a**	H	63
2	**1a**	O	F	H	$Br(CH_2)_2Br$	**3b**	Br	55
3	**1a**	O	F	H	$ClCO_2Et$	**3c**	CO_2Et	57
4	**1b**	O	Cl	OMe	4-MeC_6H_4CHO	**3d**	4-MeC_6H_4CO	73[b]
5	**1b**	O	Cl	OMe	$ClCO_2Et$	**3e**	CO_2Et	68
6	**1c**	NMe	F	H	Ph_2S_2	**4a**	SPh	36[c]
7	**1c**	NMe	F	H	$ClCO_2Et$	**4b**	CO_2Et	70
8	**1d**	$NCH_2CH{=}CH_2$	F	H	$Br(CH_2)_2Br$	**5a**	Br	72
9	**1d**	$NCH_2CH{=}CH_2$	F	H	$ClCO_2Et$	**5b**	CHO	65[d]

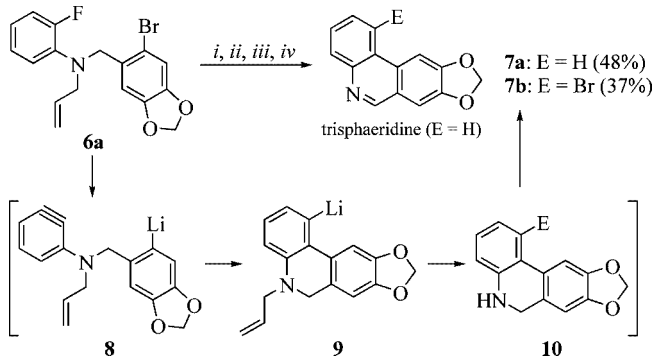
[a] Isolated yields after chromatography based on starting material **1**. [b] 4 equiv. of PCC were used. [c] Lower yield is probably due to further oxidation of the thioether group. [d] 2 equiv. of PCC were used.

after the initial benzylic oxidation. The synthesis of 1-formylphenanthridine **5b** was carried out by treatment of **1d** with *t*BuLi and ethyl chloroformate as the electrophile. The deallylation process also reduced the ethoxycarbonyl group to a hydroxymethyl group, and the final reaction with PCC led to dehydrogenation and oxidation of the hydroxymethyl group to a formyl functionality.

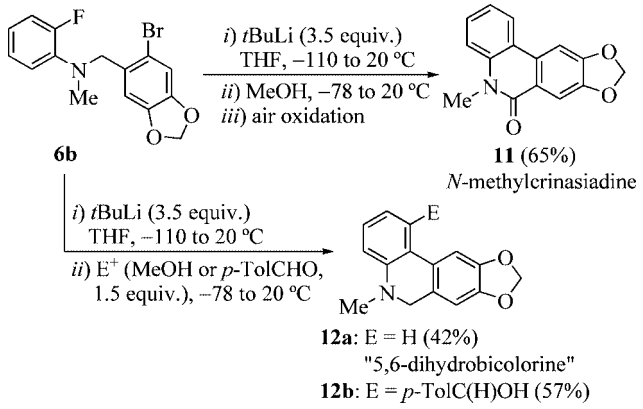
It is interesting to remark that in all cases, final regioselectively functionalized heterocycles **3**–**5** were obtained in moderate-to-good overall yields relative to easily available starting compounds **1** without the isolation of any intermediate product. For instance, the previously reported synthesis of 1-bromophenathridine **5a** has been performed in several inefficient steps.[28]

The development of this convenient and efficient synthetic route to phenanthridines[29] led us to consider testing it in the synthesis of trisphaeridine, a phenanthridine alkaloid from the *Amaryllidaceae* plant family.[14] Taking into account the preparation of phenanthridines **5**, we envisaged that *N*-allyl-*N*-(2-bromo-4,5-methylenedioxybenzyl)-2-fluoroaniline (**6a**) could be a suitable precursor for the synthesis of trisphaeridine (Scheme 3). Alkylation of the lithium amide of readily available *N*-allyl-2-fluoroaniline[12b] with 2-bromo-4,5-methylenedioxybenzyl bromide[30] afforded tertiary amine **6a** in 78% yield.[31] To our delight, when we subjected amine **6a** to the above referred reaction conditions, trisphaeridine **7a** was isolated in good overall yield without isolation of any intermediate product (Scheme 3). First, treatment of **6a** with *t*BuLi from –110 °C to room temperature gives rise to benzyne-tethered aryllithium **8** which undergoes an anionic cyclization leading to organolithium **9**. Quenching of the reaction with methanol and removal of the allyl group with DIBAL-H then affords dihydrophenanthridine derivative **10**, which on dehydrogenation with PCC gives rise to isolated phenanthridine **7a**. Their physical and spectroscopic data were identical with those of natural and synthetic trisphaeridine in all respects.[32] Interestingly, by using this methodology it is possible to access to functionalized analogues of this natural product substituted at C-1 by simple treatment of intermediate anion **9** with other electrophiles. In this way, potentially useful bromine-substituted phenanthridine **7b** could be regioselectively obtained (Scheme 3). This result also supports the intermediacy of proposed organolithium **9**.

To examine the general applicability of this methodology for the synthesis of phenanthridine alkaloids, we next attempted the synthesis of *N*-methylcrinasiadine (Scheme 1).[15] With this goal in mind we synthesized amine **6b**[31] and subjected it to the usual anionic cyclization reaction conditions (Scheme 4). After quenching with methanol, dihydrophenanthridine intermediate **12a** proved to be unstable and, upon heating, underwent air oxidation to give *N*-methylcrinasiadine alkaloid **11** in good overall yield (Scheme 4).[32] Despite the instability of **12a** and because of the controversy existing in the literature about this compound, we also isolated and characterized it. In 1990, during the course of an alkaloidal investigation on Spanish *Amaryllidaceae*, Codina and coworkers isolated a new alkaloid that they named 5,6-dihydrobicolorine and, on the basis of the NMR spectroscopic data, assigned dihydrophenanthridine structure **12a**.[33] Four years later, Banwell and coworkers developed a three-step synthesis of **12a**[34] and showed that their synthetic material was spectroscopically different from the natural product previously characterized as 5,6-dihydrobicolorine. A comparison of our spectroscopic data[32] for **12a** with the data reported by Codina[33] and Banwell,[34a] respectively, revealed that the first proposed structure of 5,6-dihydrobicolorine is not represented by compound **12a** and so, we corroborated the conclusions outlined by Banwell in his paper. Again, a regioselectively functionalized derivative of the dihydrophenanthridine parent, **12b**, could be obtained by quenching the reaction with a selected electrophile (Scheme 4).



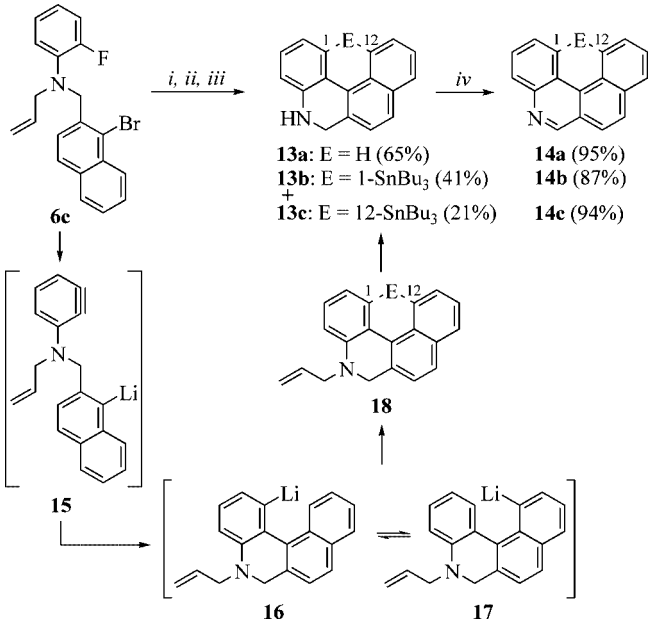
Scheme 3. Synthesis of trisphaeridine **7a**; reagents and conditions: *i*) *t*BuLi (3.5 equiv.), THF, –110 to 20 °C; *ii*) E^+ (MeOH, excess or $Br(CH_2)_2Br$, 1.5 equiv.), –78 to 20 °C; *iii*) DIBAL-H (1.5 equiv.), $[NiCl_2(dppp)]$ (4 mol-%), toluene, 20 °C; *iv*) PCC (1 equiv.), CH_2Cl_2, reflux.



Scheme 4. Synthesis of *N*-methylcrinasiadine **11** and the putative structure of 5,6-dihydrobicolorine **12a**.

Because of the biological significance of benzo-fused phenanthridine alkaloids,[35] we decided to check if our methodology could be applied to the synthesis of benzo[*k*]-phenanthridines.[36] With this idea in mind, *N*-allyl-*N*-(1-bromo-2-naphthylmethyl)-2-fluoroaniline (**6c**) was prepared by alkylation of *N*-allyl-2-fluoroaniline with 1-bromo-2-bromomethylnaphthalene.[31] Treatment of **6c** with *t*BuLi (3.5 equiv.) in THF cooled at –110 °C, warming to room

temperature, and further addition of MeOH gave rise to 5-allyl-5,6-dihydrobenzo[*k*]phenanthridine[37] (**18a**) (E = H) through anionic cyclization of benzyne intermediate **15** (Scheme 5). Deallylated dihydrobenzo[*k*]phenanthridine **13a** was easily obtained in good overall yield in an analogous way as described for phenanthridine synthesis (DIBAL-H in the presence of a catalytic amount of [$NiCl_2$(dppp)]). Benzo[*k*]phenanthridine **14a** was then obtained almost quantitatively by dehydrogenation with PCC (Scheme 5). Next, we tried to prepare a functionalized benzo[*k*]phenanthridine derivative, and it was carried out by trapping supposed organolithium **16**, generated by the anionic cyclization on benzyne intermediate **15**, with tributyltin chloride. Surprisingly, after deallylation two different regioisomers **13b** and **13c** were obtained in ca. 2:1 ratio. Major isomer **13b** was functionalized at C-1, whereas **13c** was functionalized at C-12. Again, dehydrogenation of **13b**,**c** under treatment with PCC gave rise to tributyltin-substituted benzo[*k*]phenanthridines **14b**,**c** in very good yields (Scheme 5).



Scheme 5. Synthesis of dihydrobenzo[*k*]phenanthridines **13** and benzo[*k*]phenanthridines **14**; reagents and conditions: *i*) *t*BuLi (3.5 equiv.), THF, –110 to 20 °C; *ii*) E^+ (1.5 equiv.), –78 to 20 °C; *iii*) DIBAL-H (1.5 equiv.), [$NiCl_2$(dppp)] (4 mol-%), toluene, 20 °C; *iv*) PCC (1 equiv.), CH_2Cl_2, reflux.

A proposal that accounts for the formation of two regioisomeric compounds **13** is outlined in Scheme 5. Expected cyclized organolithium **16** has the lithium atom at C-1 but it could be translocated[38] from C-1 to C-12 to afford organolithium **17**. We think that the ease of this C-[1,5] lithium shift[39] can be attributed to the steric situation in organolithium **16**. An equilibrium between both anionic intermediates **16** and **17** could take place, and so, a mixture of regioisomers **13b**,**c** is obtained after quenching with the selected electrophile (Scheme 5).

Conclusions

In summary, we have demonstrated a simple synthetic procedure for the preparation of phenanthrene-type heterocycles. This anionic cyclization provides an efficient method for the synthesis of dibenzopyranones, phenanthridinones, and phenanthridines. In contrast with other methods, our procedure allows the regioselective introduction of functional groups at C-1 in the cyclization step. On the basis of this methodology, concise syntheses of phenanthridine alkaloids trisphaeridine and *N*-methylcrinasiadine have been developed.

Experimental Section

General Remarks: Reactions requiring an inert atmosphere were carried out under an atmosphere of dry nitrogen in oven-dried glassware. THF was continuously refluxed and freshly distilled from sodium/benzophenone ketyl immediately prior to use. Flash column chromatography was carried out on silica gel 230–400 mesh. Compounds were visualized on analytical thin layer chromatograms (TLC) by UV light (254 nm) and stained with a solution of phosphomolybdic acid. Melting points were measured with a Büchi-Tottoli apparatus with open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with 400, 300, or 200 MHz Varian spectrometers with $CDCl_3$ (δ = 7.16 ppm in ^{1}H NMR spectra and δ = 76.95 ppm in ^{13}C NMR spectra) or [D_6]DMSO (δ = 2.50 ppm in ^{1}H NMR spectra and δ = 39.52 ppm in ^{13}C NMR spectra) as internal standards by use of the DEPT pulse sequence. GC–MS analyses were performed with an HP 6890N/5973 equipped with an HP-5MS column, with a gradient of 150–300 °C (30 °C/min step), and the low-resolution electron impact mass spectra (EI-LRMS) were obtained at 70 eV (only the molecular ions and/or base peaks are given). High-resolution mass spectrometry was carried out with a Micromass Autospec spectrometer. Elemental analyses were performed with Perkin–Elmer and LECO elemental analyzers. Only the most important IR absorptions are given. All commercially available reagents were used without further purification and were purchased from Aldrich Chemical Co. or Acros Organics. *t*BuLi was used as a 1.5 M solution in pentane. BuLi was used as a 2.5 M solution in hexane. Compounds **1** were synthesized in our previous work.[12b]

General Procedure for the Synthesis of 1-Functionalized 6*H*-Dibenzo[*b*,*d*]pyran-6-ones 3 and 5-Methyl-5*H*-phenanthridin-6-ones 4: A solution of starting ether **1a**,**b** or amine **1c** (2 mmol) in THF (15 mL) was treated with *t*BuLi (4.4 mL, 6.6 mmol for **1a**,**b** or 4.7 mL, 7 mmol for **1c**) at –110 °C.[12b] The reaction mixture was stirred for 15 min at this temperature, and the cooling bath was removed to allow the reaction to reach room temperature for 30 min. The reaction mixture was re-cooled to –78 °C, and the corresponding electrophile (3 mmol) was added. The mixture was allowed to reach room temperature and stirred for 3 h. The mixture was then quenched with water and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (20 mL) and treated with PCC (0.431 g, 2 mmol). The reaction mixture was stirred under reflux for 1 h and then another portion of PCC (0.862 g, 4 mmol) was added and the stirring continued under reflux for 24 h. After cooling to room temperature, the precipitate was filtered through a Celite plug and washed with CH_2Cl_2 (4 × 10 mL). The resulting solution was washed with brine, dried, and the solvents evaporated to dryness.

Column chromatography with hexane/EtOAc as the eluent afforded products **3** and **4**.

1-Bromo-6*H*-benzo[*c*]chromen-6-one (3b): Treatment of ether **1a** (0.562 g, 2 mmol) with *t*BuLi (4.4 mL, 6.6 mmol) was followed by the addition of 1,2-dibromoethane (0.564 g, 3 mmol). Further reaction with PCC (1.293 g, 6 mmol) in CH_2Cl_2 (20 mL) heated at reflux and workup as described above yielded **3b** (0.303 g, 55%) as a white solid. M.p. 173–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.46 (d, J = 8.4 Hz, 1 H), 8.44 (dd, J = 8.0, 1.6 Hz, 1 H), 7.84 (td, J = 8.4, 1.6 Hz, 1 H), 7.65–7.58 (m, 2 H), 7.34 (dd, J = 8.0, 1.2 Hz, 1 H), 7.24 (t, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.3 (C), 152.5 (C), 133.9 (CH), 133.8 (C), 132.2 (CH), 130.6 (CH), 129.9 (CH), 129.2 (CH), 125.7 (CH), 121.9 (C), 119.0 (C), 117.7 (CH), 117.5 (C) ppm. LRMS (70eV, EI): *m*/*z* (%) = 276 (100) $[M + 2]^+$, 274 (100) $[M]^+$. IR (KBr): $\tilde{\nu}$ = 3071, 1735, 1600, 1413, 1223, 924, 706 cm^{-1}. $C_{13}H_7BrO_2$ (275.1): calcd. C 56.76, H 2.56; found C 56.94, H 2.61.

General Procedure for the Synthesis of 1-Functionalized Phenanthridines 5: A solution of amine **1d** (0.640 g, 2 mmol) in THF (15 mL) was treated with *t*BuLi (4.7 mL, 7 mmol) at –110 °C. The reaction mixture was stirred for 15 min at this temperature and the cooling bath was then removed to allow the mixture to reach room temperature for 30 min. The reaction mixture was re-cooled to –78 °C and the corresponding electrophile (3 mmol) was added. After 15 min at this temperature, the reaction was allowed to reach room temperature and stirring was continued for 3 h. The mixture was quenched with water, extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with saturated aqueous Na_2CO_3 and dried with anhydrous Na_2SO_4. The solvents were removed under reduced pressure. The residue and $[NiCl_2(dppp)]$ (0.043 g, 0.08 mmol) were dissolved in toluene (6 mL). DIBAL-H (2 mL, 1.5 M solution in toluene, 3 mmol for **5a**, or 4.7 mL, 7 mmol for **5b**) was added at 0 °C and the temperature was increased to room temperature. After stirring for 2 h, the mixture was treated with NaOH (0.5 M, 2 mL) and Et_2O (9 mL), stirred for 1 h, and then dried directly over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (20 mL) and treated with PCC (0.431 g, 2 mmol for **5a**, or 0.862 g, 4 mmol for **5b**). The reaction mixture was stirred under reflux for 2 h. After cooling to room temperature, the precipitate was filtered through a Celite plug and washed with CH_2Cl_2 (4 × 10 mL). The resulting solution was extracted with brine, dried with Na_2SO_4, and the solvents evaporated to dryness. Column chromatography on silica gel (hexane/EtOAc) afforded compounds **5**.

1-Bromophenanthridine (5a): Treatment of amine **1d** (0.640 g, 2 mmol) with *t*BuLi (4.7 mL, 7 mmol) was followed by the addition of 1,2-dibromoethane (0.564 g, 3 mmol). The residue was treated with DIBAL-H (2.0 mL, 3 mmol) and $[NiCl_2(dppp)]$ (0.04 g, 0.08 mmol). Further reaction with PCC (0.431 g, 2 mmol) in CH_2Cl_2 (20 mL) at reflux and workup as described above yielded **5a** (0.395 g, 72%) as a white solid. M.p. 101–103 °C (ref.[28b] 97–99 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.93 (d, J = 8.8 Hz, 1 H), 9.16 (s, 1 H), 8.11 (dd, J = 8.0, 1.6 Hz, 1 H), 7.94 (dd, J = 8.0, 1.6 Hz, 1 H), 7.91 (dd, J = 8.0, 1.6 Hz, 1 H), 7.81–7.75 (m, 1 H), 7.65 (td, J = 8.0, 7.4 Hz, 1 H), 7.45 (t, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 154.2 (CH), 146.5 (C), 134.6 (CH), 131.7 (C), 130.5 (CH), 130.0 (CH), 128.7 (CH), 128.2 (CH), 127.7 (CH), 127.0 (C), 125.4 (CH), 122.9 (C), 118.5 (C) ppm. LRMS (70eV, EI): *m*/*z* (%) = 259 (100) $[M + 2]^+$, 257 (100) $[M]^+$. IR (KBr): $\tilde{\nu}$ = 1584, 1553, 908, 807, 753, 613 cm^{-1}. HRMS: calcd. for $C_{13}H_8BrN$ 256.9840; found 256.9848.

General Procedure for the Synthesis of Amines 6: A solution of the corresponding *N*-alkyl-2-fluoroaniline (10 mmol) in THF (15 mL) was treated with BuLi (4 mL, 10 mmol) at –50 °C. The reaction mixture was stirred for 15 min, allowed to reach room temperature, and stirring was continued for 45 min. The reaction mixture was cooled to –50 °C and the corresponding dibromo derivative (10 mmol) was added. After 15 min at this temperature, the reaction was warmed up and stirring was continued for 5 h. The mixture was quenched with water, extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with saturated aqueous Na_2CO_3 and dried with anhydrous Na_2SO_4. The solvents were removed under vacuum and the residue was purified by silica gel column chromatography (hexane/EtOAc) to afford the corresponding tertiary amine.

***N*-Allyl-*N*-(2-bromo-4,5-methylenedioxybenzyl)-2-fluoroaniline (6a):** Treatment of *N*-allyl-2-fluoroaniline[12b] (1.51 g, 10 mmol) with BuLi (4 mL, 10 mmol) was followed by the addition of 2-bromo-4,5-methylenedioxybenzyl bromide[30] (2.94 g, 10 mmol). Workup as above yielded **6a** (2.84 g, 78%) as a white solid. M.p. 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05–6.95 (m, 4 H), 6.90–6.82 (m, 2 H), 5.93 (s, 2 H), 5.94–5.86 (m, 1 H), 5.23–5.15 (m, 2 H), 4.33 (s, 2 H), 3.82 (d, J = 5.6 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 155.0 (d, J = 242.9 Hz, C), 147.5 (C), 147.1 (C), 138.0 (d, J = 7.6 Hz, C), 134.3 (CH), 131.0 (C), 124.1 (CH), 121.1 (d, J = 7.8 Hz, CH), 120.1 (CH), 117.5 (d, J = 3.1 Hz, CH_2), 116.3 (d, J = 21.5 Hz, CH), 113.1 (C), 112.5 (CH), 108.9 (CH), 101.5 (CH_2), 55.5 (d, J = 3.0 Hz, CH_2), 55.4 (d, J = 3.8 Hz, CH_2) ppm. LRMS (70eV, EI): *m*/*z* (%) = 365 (2) $[M + 2]^+$, 363 (2) $[M]^+$, 215 (99), 213 (100). $C_{17}H_{15}BrFNO_2$ (364.2): calcd. C 56.06, H 4.15, N 3.85; found C 56.19, H 4.21, N 3.80.

Synthesis of [1,3]Dioxolo[4,5-*j*]phenanthridine (Trisphaeridine) (7a) and 1-Bromo[1,3]dioxolo[4,5-*j*]phenanthridine (7b): A solution of amine **6a** (0.728 g, 2 mmol) in THF (15 mL) was treated with *t*BuLi (4.7 mL, 7 mmol) at –110 °C. The reaction mixture was stirred for 15 min at this temperature and the cooling bath was then removed to allow the mixture to reach room temperature for 30 min. The reaction mixture was re-cooled to –78 °C and the corresponding electrophile (3 mmol for 1,2-dibromoethane or excess for MeOH) was added. After 15 min at this temperature, the reaction was allowed to reach room temperature and stirring was continued for 3 h. The mixture was quenched with water, extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with saturated aqueous Na_2CO_3 and dried with anhydrous Na_2SO_4. The solvents were removed under reduced pressure. The residue and $[NiCl_2(dppp)]$ (0.043 g, 0.08 mmol) were dissolved in toluene (6 mL). DIBAL-H (2 mL, 1.5 M solution in toluene, 3 mmol) was added at 0 °C and the temperature was increased to room temperature. After stirring for 2 h, the mixture was treated with NaOH (0.5 M, 2 mL) and Et_2O (9 mL) for 1 h and it was then dried directly over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (20 mL) and it was treated with PCC (0.431 g, 2 mmol). The reaction mixture was stirred under reflux for 2 h. After cooling to room temperature, the precipitate was filtered through a Celite plug and washed with CH_2Cl_2 (4 × 10 mL). The resulting solution was extracted with brine, dried with Na_2SO_4, and the solvents evaporated to dryness. Column chromatography (hexane/EtOAc) afforded compounds **7**.

Trisphaeridine [1,3]Dioxolo[4,5-*j*]phenanthridine (7a): Treatment of amine **6a** (0.728 g, 2 mmol) with *t*BuLi (4.7 mL, 7 mmol) was followed by the addition of MeOH (excess). The residue was treated with DIBAL-H (2.0 mL, 3 mmol) and $[NiCl_2(dppp)]$ (0.04 g, 0.08 mmol). Workup as above yielded **7a** (0.214 g, 48%) as a white solid. M.p. 138–140 °C (ref.[34b] 144.5–145 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.08 (s, 1 H), 8.37 (dd, J = 8.4, 1.2 Hz, 1

H), 8.13 (dd, J = 7.4, 1.2 Hz, 1 H), 7.91 (s, 1 H), 7.68 (td, J = 7.5, 1.2 Hz, 1 H), 7.62 (td, J = 7.5, 1.5 Hz, 1 H), 7.33 (s, 1 H), 6.17 (s, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 151.7 (CH), 151.5 (C), 148.2 (C), 144.0 (C), 130.3 (C), 130.0 (CH), 128.0 (CH), 126.7 (CH), 124.3 (C), 123.0 (C), 122.0 (CH), 105.5 (CH), 101.9 (CH_2), 99.9 (CH) ppm. LRMS (70eV, EI): m/z (%) = 223 (100) $[M]^+$. IR (KBr): $\tilde{\nu}$ = 2904, 1615, 1576, 1499, 1456, 1246, 831 cm^{-1}. HRMS: calcd. for $C_{14}H_9NO_2$ 223.0633; found 223.0626.

Synthesis of 5-Methyl-[1,3]dioxolo[4,5-*j*]phenanthridin-6(5*H*)-one (*N*-Methylcrinasiadine) (11) and 5,6-Dihydro-5-methyl[1,3]dioxolo[4,5-*j*]phenanthridines (12): A solution of amine **6b** (0.676 g, 2 mmol) in THF (15 mL) was treated with *t*BuLi (4.7 mL, 7 mmol) at –110 °C. The reaction mixture was stirred for 15 min at this temperature and the cooling bath was then removed to allow the mixture to reach room temperature for 30 min. The reaction mixture was re-cooled to –78 °C and the corresponding electrophile (3 mmol for *p*-tolualdehyde or excess for MeOH) was added. After 15 min at this temperature, the reaction was allowed to reach room temperature and stirring was continued for 3 h. The mixture was quenched with water, extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with saturated aqueous Na_2CO_3 and dried with anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography (hexane/EtOAc) to afford compounds **12**. To obtain **11**, crude **12a** was heated in an oven until a temperature of 250 °C was reached. Upon cooling, the residue was purified by column chromatography (hexane/EtOAc) to afford compound **11**.

5-Methyl-[1,3]dioxolo[4,5-*j*]phenanthridin-6(5*H*)-one (*N*-Methylcrinasiadine) (11): Treatment of amine **6b** (0.676 g, 2 mmol) with *t*BuLi (4.7 mL, 7 mmol) was followed by the addition of MeOH (excess). Workup as above yielded crude **12a** which was heated to 250 °C. Purification by column chromatography afforded **11** (0.329 g, 65%) as a white crystalline solid. M.p. 246–248 °C (ref.[34b] 247.5–248.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (dd, J = 8.2, 1.2 Hz, 1 H), 7.91 (s, 1 H), 7.63 (s, 1 H), 7.53 (ddd, J = 8.2, 7.0, 1.2 Hz, 1 H), 7.41 (dd, J = 8.2, 1.2 Hz, 1 H), 7.31 (ddd, J = 8.2, 7.0, 1.2 Hz, 1 H), 6.13 (s, 2 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 160.9 (C), 152.1 (C), 148.3 (C), 137.3 (C), 130.3 (C), 128.8 (CH), 122.8 (CH), 122.3 (CH), 121.2 (C), 119.1 (C), 115.0 (CH), 106.9 (CH), 101.9 (CH_2), 100.4 (CH), 30.0 (CH_3) ppm. LRMS (70eV, EI): m/z (%) = 253 (100) $[M]^+$. IR (KBr): $\tilde{\nu}$ = 2919, 1650, 1482, 1460, 1346, 1323, 1026, 932 cm^{-1}. HRMS: calcd. for $C_{15}H_{11}NO_3$ 253.0739; found 253.0745.

Preparation of Dihydrobenzo[*k*]phenanthridines 13a–c: A solution of amine **6c** (0.741 g, 2 mmol) in THF (15 mL) was treated with *t*BuLi (4.7 mL, 7 mmol) at –110 °C. The reaction was stirred for 15 min at this temperature and the cooling bath was then removed to allow the reaction to reach room temperature for 30 min. The mixture was re-cooled to –78 °C, and the corresponding electrophile (3 mmol) was added. The mixture was allowed to reach room temperature and the reaction was stirred for 3 h. The mixture was quenched with water, extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with saturated aqueous Na_2CO_3 and dried with anhydrous Na_2SO_4. The solvents were removed under reduced pressure. For the removal of the allyl group, the residue and [$NiCl_2$(dppp)] (0.043 g, 0.08 mmol) were dissolved in toluene (6 mL). DIBAL-H (2 mL, 1.5 M solution in toluene, 3 mmol) was added at 0 °C and the temperature was increased to room temperature. After stirring for 2 h, the mixture was treated with NaOH (0.5 M, 2 mL) and Et_2O (9 mL) for 1 h and it was then dried directly over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc) to afford compounds **13**.

5,6-Dihydrobenzo[*k*]phenanthridine (13a): Treatment of amine **6c** (0.741 g, 2 mmol) with *t*BuLi (4.7 mL, 7 mmol) was followed by the addition of MeOH (excess). The residue was treated with DIBAL-H (2.0 mL, 3 mmol) and [$NiCl_2$(dppp)] (0.04 g, 0.08 mmol). Workup as above yielded **13a** (0.301 g, 65%) as a colorless oil. R_f = 0.32 (hexane/EtOAc, 5:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.68–8.61 (m, 1 H), 8.04 (dd, J = 8.0, 1.2 Hz, 1 H), 7.95–7.88 (m, 1 H), 7.76 (d, J = 8.2 Hz, 1 H), 7.61–7.46 (m, 2 H), 7.29 (d, J = 8.6 Hz, 1 H), 7.21 (dd, J = 7.5, 1.6 Hz, 1 H), 7.04 (td, J = 7.6, 1.2 Hz, 1 H), 6.87 (dd, J = 7.6, 1.2 Hz, 1 H), 4.34 (s, 2 H), 3.90 (br. s, 1 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 148.2 (C), 134.3 (C), 134.1 (C), 129.5 (C), 128.8 (C), 128.62 (CH), 128.60 (CH), 127.9 (CH), 127.4 (CH), 126.2 (CH), 125.6 (CH), 125.1 (CH), 123.9 (CH), 123.4 (C), 119.0 (CH), 115.6 (CH), 47.8 (CH_2) ppm. LRMS (70eV, EI): m/z (%) = 231 (45) $[M^+]$, 230 (100). IR (KBr): $\tilde{\nu}$ = 3440, 3048, 1584, 1491, 765 cm^{-1}. HRMS: calcd. for $C_{17}H_{13}N$ 231.1048; found 231.1057.

Preparation of Benzo[*k*]phenanthridines 14: PCC (0.108 g, 0.5 mmol) was added to a solution of corresponding dihydrophenantridine **13** (0.5 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred under reflux for 2 h. After cooling to room temperature, the precipitate was filtered through a Celite plug and washed with CH_2Cl_2 (3 × 10 mL). The resulting solution was washed with brine, dried, and the solvents evaporated to dryness. Silica gel column chromatography (hexane/EtOAc) afforded products **14**.

Benzo[*k*]phenanthridine (14a): Dihydrobenzophenanthridine **13a** (0.116 g, 0.5 mmol) was treated with PCC (0.108 g, 0.5 mmol). Workup as described above yielded **14a** (0.109 g, 95%) as a yellow solid. M.p. 108–110 °C (ref.[36b] 108–110 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.34 (br. s, 1 H), 9.16 (d, J = 8.0 Hz, 1 H), 9.07 (d, J = 8.4 Hz, 1 H), 8.33 (br. s, 1 H), 8.05 (d, J = 8.4 Hz, 1 H), 7.99 (d, J = 8.4 Hz, 1 H), 7.92 (d, J = 8.4 Hz, 1 H), 7.85–7.70 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.4 (C), 146.1 (C), 135.1 (C), 131.3 (C), 130.0 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.0 (CH), 126.9 (CH), 126.8 (CH), 125.0 (CH), 124.5 (C) ppm. LRMS (70eV, EI): m/z (%) = 229 (100) $[M^+]$. IR (KBr): $\tilde{\nu}$ = 2923, 1579, 1451, 1381, 818, 768 cm^{-1}. HRMS: calcd. for $C_{17}H_{11}N$ 229.0891; found 229.0885.

Supporting Information (see footnote on the first page of this article): Spectroscopic and characterization data for the rest of the compounds. Copies of the NMR spectra of all products and comparison of the analytical data of **12a** with the different data reported for 5,6-dihydrobicolorine. Comparison of the spectroscopic data of synthesized trisphaeridine **7a** and *N*-methylcrinasiadine **11** with those of the reported natural and synthetic products.

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[30] Prepared from piperonyl alcohol by treatment with Br_2 (1.5 equiv.) in $CHCl_3$. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.00 (s, 1 H), 6.89 (s, 1 H), 5.98 (s, 2 H), 4.54 (s, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 148.7, 147.6, 129.9, 115.6, 113.1, 110.5, 102.1, 34.1 ppm. LRMS (70eV, EI): *m/z* (%) = 296 (3) $[M + 4]^+$, 294 (7) $[M + 2]^+$, 292 (3) $[M]^+$, 215 (100), 213 (100).

[31] See Experimental Section for the synthesis of tertiary amines **6**.

[32] See Supporting Information for comparison of NMR spectroscopic data.

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[36] Synthesis of benzo[*k*]phenanthridines: a) By photocyclization of 4-phenyl-3-vinylquinolines, see: K. Veeramani, P. Shanmugam, *Indian J. Chem.* **1987**, *26B*, 116–121; b) By cyclization of

aryl formamides, see: J. H. Boyer, J. R. Patel, *Synthesis* **1978**, 205.

[37] 5-Allyl-5,6-dihydrobenzo[*k*]phenanthridine (**18a**): yellow solid. M.p. 131–133 °C. ^{1}H NMR (80 MHz, $CDCl_3$): δ = 8.64–8.46 (m, 1 H), 8.06–6.80 (m, 9 H), 6.26–5.70 (m, 1 H), 5.50–5.14 (m, 2 H), 4.14 (s, 2 H), 3.90 (dt, J = 5.8, 1.6 Hz, 2 H) ppm. ^{13}C NMR (20.2 MHz, $CDCl_3$): δ = 148.6, 134.8, 134.3, 133.9, 129.0, 128.8, 128.7, 128.2, 127.6, 127.3, 126.2, 125.8, 125.1, 124.8, 123.6, 118.2, 118.1, 113.6, 53.4, 53.3 ppm. LRMS (70eV, EI): *m*/*z* (%) = 271 (42) $[M]^+$, 41 (100). IR (KBr): $\tilde{\nu}$ = 3071, 1631, 1600, 1370, 749 cm^{-1}.

[38] For the introduction of the anion translocation concept, see: A. Ahmed, J. Clayden, M. Rowley, *Chem. Commun.* **1998**, 297–298.

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