JOC The Journal of Organic Chemistry

Article

Total Synthesis of Calothrixin A & B by Exploiting Alkylquinone Tautomerization

Luis M. Mori-Quiroz, Madeline M. Dekarske, Austin B. Prinkki, and Michael D. Clift

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 31 Oct 2017

ACS Publications

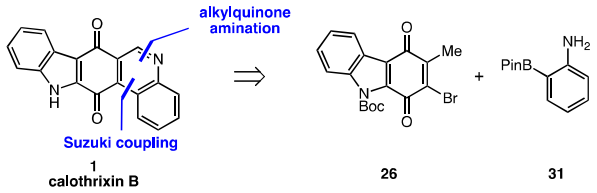
The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Total Synthesis of Calothrixin A & B by Exploiting Alkylquinone Tautomerization

Luis M. Mori-Quiroz, Madeline M. Dekarske, Austin B. Prinkki and Michael D. Clift*

Department of Chemistry, The University of Kansas, Lawrence, KS, 66045

mclift@ku.edu



ABSTRACT: The pentacyclic alkaloid calothrixin B (**1**) has been synthesized in 5 steps from murrayaquinone A (**9**). The key step involved the union of boryl aniline **31** with brominated murrayaquinone A (**26**). In this transformation, alkylquinone **26** undergoes tautomerization to a quinone methide which is intercepted by boryl aniline **31** to forge a new C–N bond. An intramolecular Suzuki coupling, followed by dehydrogenative aromatization, completed the synthesis of calothrixin B. Subsequent N-oxidation of calothrixin B delivered calothrixin A. The successful synthesis of these alkaloids and the challenges that led to the development of the final synthesis plan are reported herein.

INTRODUCTION

Calothrixin B (**1**) and its N-oxide, calothrixin A (**2**), are pentacyclic alkaloids first isolated from *calothrix* cyanobacteria in 1999 by Rickards, Smith and coworkers.[1] Their structure comprises a 1,4-benzoquinone flanked by indole and quinoline scaffolds, making them unique among related phenanthridine alkaloids (Figure 1). Their interesting biological activities, including potent antimalarial and anticancer activities,[1, 2] have attracted the attention of synthetic chemists, resulting in several total and formal syntheses.[3] Although a few of these are rather concise and efficient, we believed that application of methodology developed in our lab would not only allow for a comparably short and scalable synthesis of calothrixin B, but also validate this method as a useful tool to efficiently access related phenanthridine-containing natural products and analogues possessing interesting biological activities.

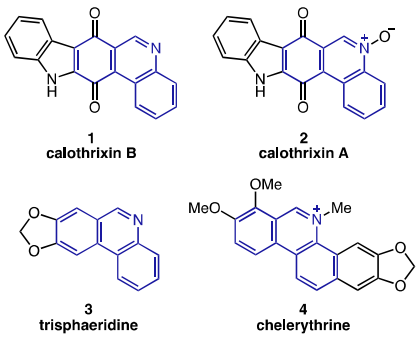


Figure 1. Representative phenanthridine-containing alkaloids.

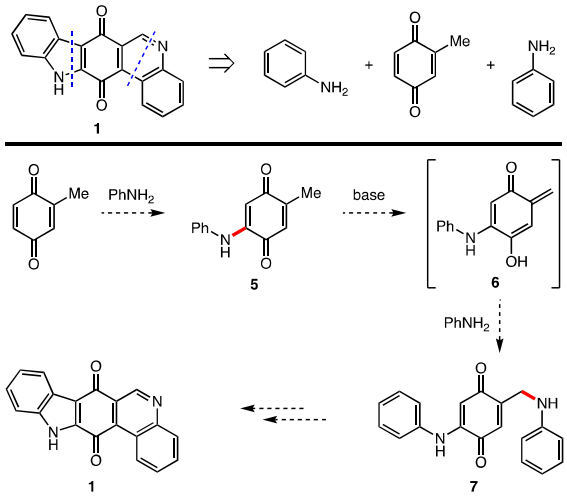
We recently reported a robust protocol to access benzylic amines from alkylquinones and primary or secondary amines.[4] The reaction proceeds by tautomerization of the alkylquinone to generate an *ortho*-quinone methide intermediate that is subsequently trapped by the amine, delivering an aminated dihydroquinone. Reactions involving alkylquinone tautomerization were first reported nearly a century ago,[5-7] but only recently has this type of reactivity been exploited to develop efficient transformations, including cycloadditions[8] and electrocyclizations (see below). Relative to other methods to generate quinone methides,[9] such as thermolysis, photolysis and elimination reactions of phenol derivatives, alkylquinone tautomerization offers several advantages: 1) it avoids the need for prior functionalization (e.g. the installation of a leaving group), effectively leading to full atom economy, 2) tautomerization typically proceeds under very mild conditions and therefore has great potential for application in complex molecule synthesis.

In the context of natural product total synthesis, alkylquinone tautomerization has been applied in a few cases involving intramolecular C–C and C–O bond forming processes. Pettus applied an alkylquinone tautomerization / intramolecular arylation sequence to the total synthesis of (±)-brazilin,[10] whereas Trauner devised ingenious alkylquinone tautomerization / electrocyclization cascades to complete the total syntheses of mollugin, microphyllaquinone, and exiguamines A and B.[11] Trauner also applied alkylquinone tautomerization in the total synthesis of rubioncolin B involving an intramolecular Diels-Alder reaction of the generated quinone methide intermediate.[12] Despite these successful examples, the amination of quinone methide intermediates has remained largely ignored and has not been applied in natural product total synthesis. We therefore set out to demonstrate the utility of alkylquinone amination as a tool for the concise and efficient assembly of alkaloid natural products by targeting calothrixin B for total synthesis.

RESULTS AND DISCUSSION

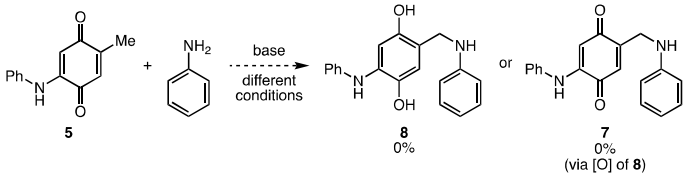
Initial synthetic plan

Our initial retrosynthetic analysis of calothrixin B involved disconnection of 2 C–C bonds and 2 C–N bonds, thus revealing three simple building blocks: methyl-*p*-benzoquinone and 2 molecules of aniline (Scheme 1). In the forward sense, the known quinone **5** is obtained by a selective conjugate addition of aniline to methyl-*p*-benzoquinone. Next, we envisioned that alkylquinone **5** would undergo tautomerization to give its corresponding quinone methide **6** followed by nucleophilic trapping with a second molecule of aniline, delivering **7** after oxidation of the dihydroquinone (not shown). A double, intramolecular dehydrogenative coupling involving intermediate **7** would complete the synthesis of calothrixin B.



Scheme 1. Retrosynthetic analysis for calothrixin B.

To test this strategy, we prepared alkylquinone **5** and explored its amination with aniline (Scheme 2); however, under a variety of reactions conditions, including those we had previously developed,[4] we were unable to detect any of the amination product **8**, or its oxidized derivative **7**. It is important to mention that **5** does undergoes amination with secondary alkylamines in modest yields, which suggested the failure to form any detectable amount of **7** or **8** is related to the attenuated nucleophilicity of aniline.

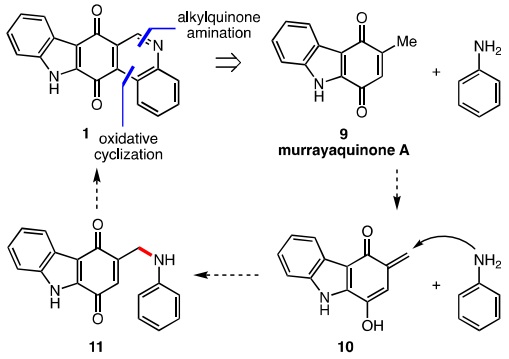


Scheme 2. Attempted amination of alkylquinone **5** with aniline.

Alternative synthetic approach

Given that amination of **5** with aniline was not possible, our original retrosynthesis was revised to focus on two key disconnections of **1**, leading back to murrayaquinone A and aniline as potential precursors (Scheme 3). In the forward sense,

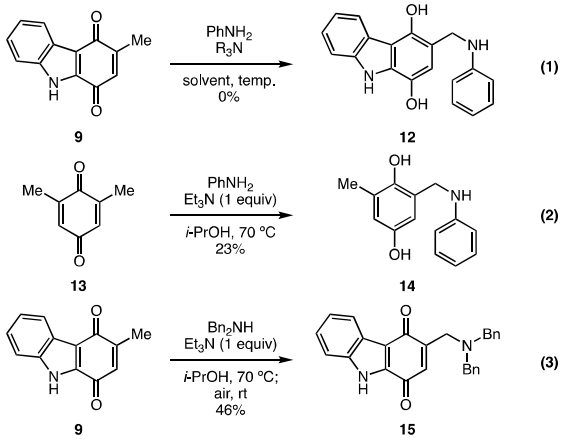
amination of alkylquinone **9** would deliver, after oxidation of the dihydroquinone (not shown), tetracyclic quinone **11**. Intermediate **11** would then undergo a metal-catalyzed intramolecular cyclization and subsequent dehydrogenation, leading to calothrixin B. Murrayaquinone A, itself a natural product isolated from the root bark of *Murraya euchrestifolia* Hayata,[13] is commercially available or prepared in two steps from aniline and methyl-*p*-benzoquinone.[14]



Scheme 3. Alternative retrosynthesis for calothrixin B leading to murrayaquinone A and aniline as building blocks.

Amination of murrayaquinone A: Preliminary experiments

We first attempted the amination of murrayaquinone A (**9**) with aniline under conditions previously optimized in our group,[4] using *iso*-propanol as a solvent and triethylamine as a base. However, the limited solubility of **9** in *iso*-propanol forced us to examine other more polar (co)solvents. Unfortunately, these experiments were unsuccessful and none of the desired aminated product (**12**) was ever observed (Scheme 4, eq. 1). Increased temperature and use of different bases led to extensive decomposition. We attributed the failure of the reaction to two factors: 1) the low nucleophilicity of aniline, and 2) slow tautomerization of **9** made other side reactions competitive, particularly electron-transfer processes that eventually led to reduction and/or decomposition of the alkylquinone **9**.

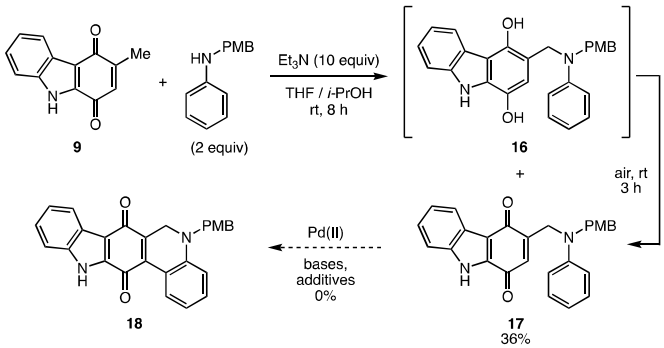


Scheme 4. Preliminary studies.

In order to test these hypotheses, we independently subjected both reactants, aniline and murrayaquinone, to the optimal amination reaction conditions with competent reaction partners (scheme 4, eq. 2 and 3). We assessed the capability of aniline as a reaction partner by testing its ability to react with 2,6-dimethylbenzoquinone (**13**), an alkylquinone that reacted cleanly with a wide range of substrates in our prior work.[4] Reaction of alkylquinone **13** with aniline led to the amination product **14** in only 23% NMR yield, together with 38% of 2,6-dimethylhydroquinone and decomposition products (scheme 4, eq. 2). In a similar way, we evaluated the competency of **9** to undergo amination with dibenzylamine, an amine that had previously reacted efficiently with a variety of alkylquinones. Reaction of **9** with dibenzylamine afforded, after oxidation upon exposure to air, 46% yield of aminated quinone **15** and 15% of recovered murrayaquinone A. These experiments illustrate the modest reactivity of **9** towards amination and the poor performance of aniline as a reaction partner for this amination reaction.

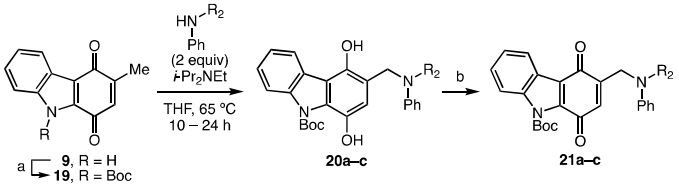
1st Generation approach: Amination of (N-Boc) murrayaquinone A (19) with N-alkyl anilines

To address these reactivity issues, we first tested the amination of murrayaquinone A (**9**) using a more nucleophilic 2º N-PMB aniline. Indeed this allowed the desired amination of **9** to proceed, affording a mixture of dihydroquinone **16** and quinone **17**. After exposure of the crude reaction mixture to air for 3 h, **17** was isolated in 36% yield (Scheme 5). Careful analysis of the reaction mixture before aerobic oxidation also revealed the presence of reduced **9** (not shown). Since the reaction is run in the absence of oxygen, the formation of reduced **9** and product **17** is likely a consequence of a redox reaction between **9** (oxidant) and the initial aminated product **16** (reductant), which unproductively consumes **9**. We reasoned that using a sacrificial oxidant might oxidize the initial hydroquinone **16** to final product **17**, effectively mitigating the undesired reduction of **9**. Unfortunately, addition of organic or inorganic oxidants led to lower yields or only marginal improvement, and other attempts to improve the efficiency of the reaction were unsuccessful. Finally, we attempted the oxidative cyclization of **17** employing catalytic or stoichiometric Pd(II) salts, in the presence of different bases and oxidants; however, we only observed decomposition of **17**.



Scheme 5. Successful amination of murrayaquinone A (**9**) with N-PMB aniline and failed dehydrogenative coupling.

We recognized that the electron-rich indole of **9** may be attenuating the electrophilicity of the corresponding quinone methide and subsequently increasing the likelihood that the desired amination product **16** engages in redox reactions with the remaining starting material **9**. To address these issues, we installed a *tert*-butoxycarbonyl (Boc) group on nitrogen to reduce the electron-donating capacity of the indole (table 1). Protection of the indole under standard conditions took place efficiently (96% yield). Under optimized conditions, employing excess *i*-Pr_2NEt in THF, reaction of Boc protected murrayaquinone A (**19**) with N-alkyl aniline derivatives provided the corresponding aminated products **20a-c** in good yields (Table 1). Compound **20a** could be isolated in 79% yield (entry 1), however compounds **20b** and **20c** underwent partial oxidation to **21b** and **21c** (entries 2 and 3) during the isolation procedure and could not be purified. Complete oxidation of **20a-c** with $FeCl_3$ afforded the quinones **21a-c** in good yields (table 1).



Entry	R_2	Product 20	Yield 20 (%)	Product 21	Yield 21 (%)
1	PMB	**20a**	79	**21a**	94
2	allyl	**20b**	65[c]	**21b**	98
3	Me	**20c**	83[d]	**21c**	92

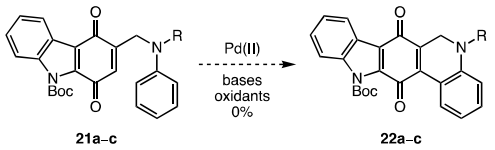
[a] Boc_2O (1.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, 96%. [b] $FeCl_3$, MeCN, rt, or Ag_2O, MeCN, rt. [c] NMR yield, 10:1 mixture of **20b** / **21b**. [d] NMR yield, 7:1 mixture of **20c** / **21c**.

Table 1. Amination of N-Boc murrayaquinone with different N-alkyl aniline derivatives and oxidation to the corresponding quinones **21a-c**.

Attempted dehydrogenative cyclization of aminated quinones

Having optimized the amination step, we then focused on the oxidative C–C bond formation (Scheme 6). Treatment of compounds **21a-c** with catalytic or stoichiometric Pd(II) salts under conditions developed for related dehydrogenative cyclizations,[15] led mostly to decomposition of the starting material. The only products that could be identified in reactions of **21a** and **21b** were N-PMB aniline and N-allyl aniline, suggesting C–N bond cleavage as a competitive side reaction. We wondered whether the N-alkyl groups were detrimental for the desired cyclization and therefore attempted removing them under standard oxidative (Table 1, **21a**, R_2=PMB) or reductive (**20a** and **20b**, R_2=PMB and allyl, respectively) conditions but this led to

complete decomposition. Given that the dehydrogenative cyclization of compounds **21** did not take place at all, we decided to once again modify our synthetic strategy.



Scheme 6. Attempted dehydrogenative cyclization of aminated murrayaquinone A derivatives **21a−c**.

2nd Generation approach: synthesis of brominated precursors to avoid unsuccessful dehydrogenative coupling

Although we were able to establish optimal conditions for the amination of N-Boc murrayaquinone (**9**), the final dehydrogenative cyclization proved to be more challenging than expected. We sought to solve this problem by introducing a bromo substituent either at the ortho position of the aniline (as in **24**, Figure 2), or at the quinone ring (as in **28**). We expected that clean oxidative addition of a Pd(0) catalyst to the C–Br bond in either **24** or **28** would lead to an organopalladium (II) species capable of undergoing intramolecular C–H activation and subsequent reductive elimination to forge the final pyridyl ring of calothrixin B.[16]

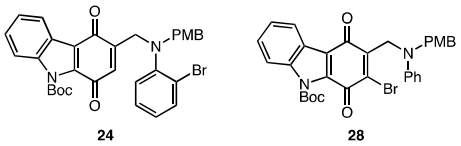
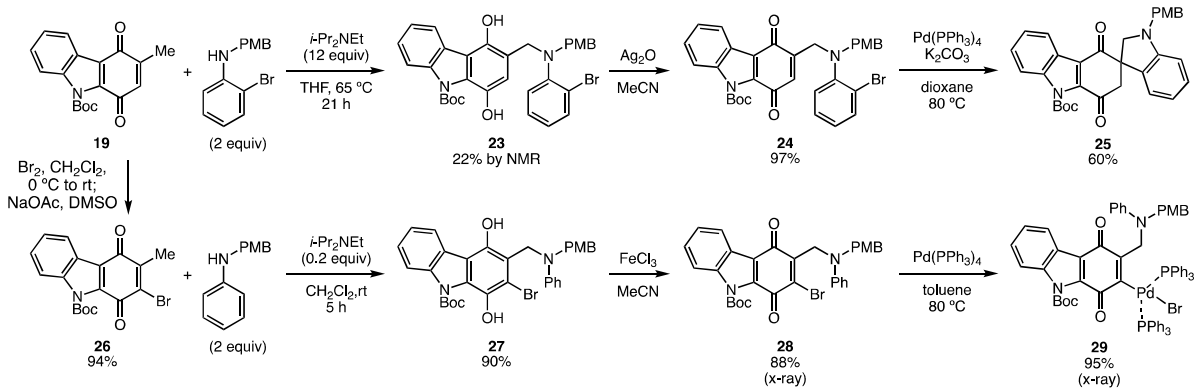


Figure 2. Brominated derivatives **24** and **28** as potential precursors to enable formation of the pyridyl ring.

In order to access **24**, we first subjected **19** to amination with N-PMB-2-bromoaniline under previously optimized conditions (scheme 7). Unfortunately the amination proceeded sluggishly to give **23** in only 22% yield, presumably due to both decreased nucleophilicity of the amine and steric hindrance introduced by the 2-bromo substituent. Modification of the reaction conditions did not improve the yield of the reaction; for instance, running the reaction at higher temperature (dioxane, 80 ºC) led to significant unproductive dimerization of the alkylquinone (**D1**, Figure 3).[17] The dimerization of alkylquinones by [4+2] cycloaddition under basic conditions has been previously observed.[18]



Scheme 7. Synthesis of aminated quinones **24** and **28** and attempted cyclization.

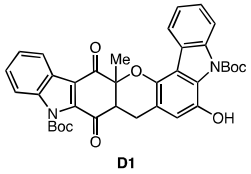
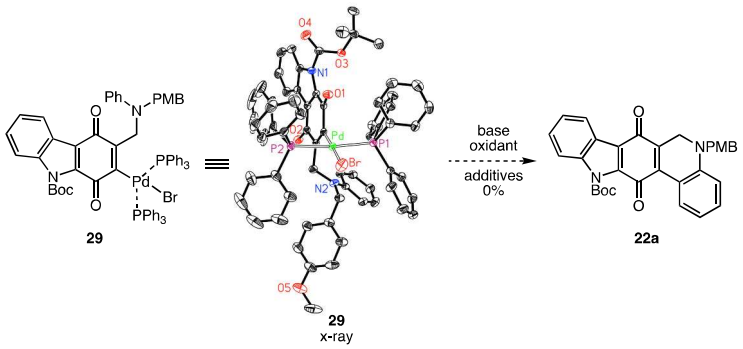


Figure 3. Competitive cycloaddition of quinone methide derived from **19** led to **D1.**

Despite the low yields, we isolated compound **23** and oxidized it to the corresponding quinone **24** in 97% yield. Treatment of **24** with $Pd(PPh_3)_4$ led to regioselective 5-exo-trig cyclization to give the spirocyclic product **25**. Given that the inherent regioselectivity of the carbopalladation event would likely be difficult to overcome,[19] we decided to pursue the alternative route by targeting quinone **28**.

Towards that end, bromination of N-Boc murrayaquinone A proceeded efficiently to give **26** in 94% yield (Scheme 7). In stark contrast to reactions of **9** and **19**, the more electron deficient alkylquinone derivative **26** underwent efficient tautomerization / amination with PMB-aniline at room temperature while employing a catalytic amount of *i*-Pr_2NEt, affording hydroquinone **27** in 90% yield. Oxidation led to quinone **28** in 88% yield. We initially tested the cyclization of **28** by employing catalytic $Pd(PPh_3)_4$ under different conditions, however no cyclization was observed. Under stoichiometric conditions, oxidative addition of $Pd(PPh_3)_4$ to **28** took place cleanly (scheme 7) and we were able to isolate the Pd(II) complex **29** and confirm its structure by x-ray crystallographic analysis. Unfortunately, attempts at promoting intramolecular C–H palladation of the pendant aniline, and subsequent reductive elimination to **22a** were not successful (Scheme 8).



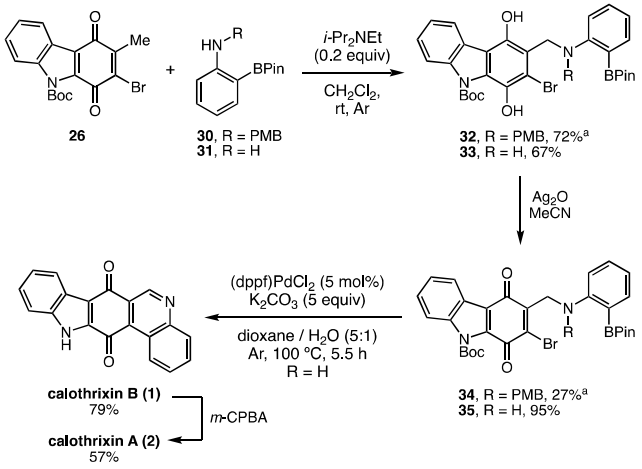
Scheme 8. Attempts at cyclizing the oxidative addition product **29**.

Although our second generation approach was not successful, we learned that brominated substrates **24** and **28** underwent efficient oxidative addition with Pd(0); however, intramolecular palladation was unsuccessful. Further, we learned that bromo-murrayaquinone A (**26**) undergoes highly efficient amination. This led as to consider a double functionalization strategy to complete the cyclization step.

3rd Generation approach: synthesis of Suzuki reaction precursors using 2-borylanilines

Given that the cyclization did not take place with our previous approaches, we decided to target doubly functionalized substrates capable of undergoing an intramolecular Suzuki reaction. Towards this end, we performed the amination of brominated alkylquinone **26** with 2-borylated anilines **30** and **31** (Scheme 9). Aniline **30** is accessible in one step from commercially available **31** by standard reductive amination with *p*-anisaldehyde. Amination of **26** with N-PMB 2-boryl aniline **30** proceeded in good yield (93%) using catalytic *i*-Pr_2NEt (20 mol%). Product **32** and its oxidized derivative **34** proved to be difficult to purify, apparently due to instability in silica or alumina. Attempts to purify **32** and **34** by recrystallization also failed.

Inability to purify **32** and **34** forced us to turn to aniline **31** as a potential reaction partner and quite surprisingly, amination of **26** took place efficiently to give compound **33** in 67% yield. The observed reactivity of **31** in the amination reaction is particularly interesting when compared with the poor reactivity of aniline and 2-bromoaniline. We suspect that resonance delocalization of the nitrogen lone pair into the aryl ring is decreased due to difficulty in attaining an optimal, parallel orientation with the π system because of the steric demand created by the adjacent BPin group; this effectively increases the nucleophilicity of nitrogen and facilitates productive amination. Hydroquinone **33** was more stable than its PMB analogue **32**, and could be purified without significant decomposition and subsequently oxidized to quinone **35** in good yield.



Scheme 9. Amination of **26** with *ortho*-boryl anilines **30** and **31** and completion of calothrixin B and A. [a] NMR yield.

Finally, treatment of **35** with catalytic (dppf)$PdCl_2$ in the presence of potassium carbonate afforded calothrixin B (**1**) in 79% overall yield (>1 g scale). The reaction conditions not only led to the desired cyclization, but also concomitant dehydrogenation of the C–N bond and Boc deprotection to afford **1**.[20] Treatment of calothrixin B with *m*-CPBA in refluxing dichloromethane afforded calothrixin A (**2**).[3a]

CONCLUSIONS

In conclusion, we have synthesized calothrixin B in 5 steps and 45% overall yield from readily available murrayaquinone A (**9**). The key step involved an efficient, *i*-Pr_2NEt catalyzed, amination of N-Boc-2-bromo murrayaquinone A (**26**) with 2-borylaniline **31**. An intramolecular Suzuki reaction, which proceeded with concomitant Boc deprotection and dehydrogenation completed the synthesis of calothrixin B. Calothrixin A was subsequently accessed using an established protocol for N-oxidation. This work has demonstrated that amination via alkylquinone tautomerization is a useful tool to the total synthesis of phenanthridine-containing natural products and we are currently pursuing the total synthesis of related alkaloids.

EXPERIMENTAL SECTION

General Information.

All moisture sensitive reactions were performed in oven-dried glassware with Teflon-coated magnetic stirring bars under Ar atmosphere. Toluene, THF, dioxane, triethylamine and dichloromethane were purified by passing the solvent through activated alumina using a solvent purification system. Commercial anhydrous diisopropylethylamine and *iso*-propanol were used as received. Column chromatography was performed using silica gel (230-400 mesh, grade 60) or activated neutral alumina (150

mesh, Brockmann I). Reactions were monitored by Thin Layer Chromatography (silica gel 60 F_{254}) and visualized using UV, or $KMnO_4$ or PMA stain solutions. ^{1}H NMR, ^{13}C NMR, ^{11}B and ^{31}P NMR spectra were recorded at room temperature on 400 and 500 MHz spectrometers. Chemical shifts are reported in ppm and referenced with respect to residual protic solvent as internal reference. Infrared spectra was recorded using a iS5 FTIR spectrometer. Mass spectra were obtained on a Micromass LCT Premier quadrupole and time-of-flight tandem mass analyzer.

2-methyl-5-(phenylamino)cyclohexa-2,5-diene-1,4-dione (5).[14a] Compound **5** was prepared following a reported procedure.[14a] A 1 L round bottom flask was charged with a magnetic stirring bar, 2-methyl-1,4-benzoquinone (6 g, 49.1 mmol, 2 equiv) and water (600 mL). The suspension was heated to ~60 ºC until most quinone dissolved and then it was cooled down for about 30 min. A solution of aniline (2.29 g, 24.6 mmol, 1 equiv) and acetic acid (2 mL) in water (20 mL) was added the mixture was vigorously stirred for 6 h. The suspension was extracted with CH_2Cl_2 (3 x 200 mL). Combined organic extracts were washed with water (100 mL), $NaHCO_{3\,(sat)}$ (2 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash silica gel chromatography (3:7 hexanes / CH_2Cl_2) and recrystallization from warm EtOAc afforded **5** (2.5 g, 48%) as a dark violet solid: mp = 153-154 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.26 (s, 1H), 7.22 – 7.16 (m, 3H), 6.57 (q, J = 1.6 Hz, 1H), 6.18 (s, 1H), 2.10 (d, J = 1.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.7, 183.8, 149.7, 142.9, 137.5, 129.6, 129.3, 125.3, 122.0, 100.9, 16.5. The spectral data is in accordance with published values.

3-methyl-1*H*-carbazole-1,4(9*H*)-dione (9, Murrayaquinone A).[14b] Murrayaquinone A (**9**) was prepared by a slight modification of a reported procedure.[14b] A 100 mL round bottom flask was charged with a magnetic stirbar, quinone **5** (544 mg, 2.55 mmol, 1 equiv), $Pd(OAc)_2$ (85.0 mg, 0.383 mmol. 0.15 equiv), $Sn(OAc)_2$ (90.6 mg, 0.383 mmol, 0.15 equiv) and acetic acid (51 mL). The flask was capped with a septum and flushed with O_2 using a balloon. The reaction mixture was heated in an oil bath at 90 ºC with vigorous stirring, attached to a O_2 balloon. After 9 h the reaction was cooled at room temperature, diluted with EtOAc (~20 mL) and filtered through celite, rinsing with EtOAc. If precipitation of the product occurred, THF was used to wash the celite. The filtrate was fully concentrated, the black residue dissolved in THF and loaded into a neutral alumina column packed with 30% EtOAc in hexanes. The column was run with 30% EtOAc in hexanes to remove the less polar impurities and then with 30-50% THF in hexanes. The impure fractions were concentrated and recrystallized from hot EtOAc. Compound **9** (299.7 mg, 56%) was obtained as a red solid: mp = 241-242 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.05 (dt, J = 7.9, 1.1 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.38 (m, 1H), 7.31 (ddd, J = 8.0, 6.9, 1.0 Hz, 1H), 6.62 (q, J = 1.7 Hz, 1H)

2.07 (d, J = 1.7 Hz, 3H); ^{13}C NMR (126 MHz, DMSO) δ 183.1, 180.1, 148.0, 137.4, 135.9, 131.6, 126.2, 123.8, 123.6, 121.6, 115.4, 113.8, 15.6. The spectral data is in accordance with published values.

2-methyl-6-((phenylamino)methyl)benzene-1,4-diol (14) and its oxidation product 2-methyl-6-((phenylimino)methyl)benzene-1,4-diol (14-ox). A dry 7 mL vial was charged with a magnetic stirbar and 2,6-dimethyl-1,4-benzoquinone (100 mg, 0.735 mmol, 1 equiv). The vial was capped and evacuated / backfilled with Ar (3 cycles). *i*-PrOH (2.5 mL) was added, followed by aniline (67 μL, 0.735 mmol, 1 equiv) and Et_3N (0.1 mL, 0.735 mmol, 1 equiv). The vial was heated in an aluminum block at 70 ºC for 2 h. The reaction was cooled at room temperature, opened to air and diluted with EtOAc (2 mL). 1,3,5-trimethoxybenzene (123.5 mg, 0.735 mmol, 1 equiv) was added and the mixture concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction showed 23% yield of benzylic amine product **14**, whose mass spectra matched the expected values. Flash silica gel chromatography (3% MeCN in hexanes) afforded it oxidized derivative, imine **14-ox** (23.4 mg, 14%) as a red oil. Spectroscopic data for **14-ox**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.41 (m, 2H), 7.30 – 7.24 (m, 3H), 6.82 (dd, J = 2.9, 0.9 Hz, 2H), 6.75 (d, J = 3.0 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 153.6, 148.1, 147.4, 129.4, 127.6, 126.9, 122.5, 121.1, 118.1, 114.7, 15.65; IR (cm^{-1}) 3361, 2920, 1622, 1601, 1488; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_2^+$ 228.1025, found 228.1036.

3-((dibenzylamino)methyl)-1*H*-carbazole-1,4(9*H*)-dione (15). A dry 7 mL vial was charged with a magnetic stirbar and quinone **9** (22 mg, 0.104 mmol, 1 equiv). The vial was capped and evacuated / backfilled with Ar (3 cycles). *i*-PrOH (0.7 mL) was added, followed by dibenzylamine (21 μL, 0.104 mmol, 1 equiv) and Et_3N (15 μL, 0.104 mmol, 1 equiv). The vial was heated in an aluminum block at 70 ºC for 2 h. The reaction was cooled at room temperature, opened to air, diluted with EtOAc (2 mL) and stirred for 12 h. 1,3,5-trimethoxybenzene (17.5 mg, 0.104 mmol, 1 equiv) was added and the mixture concentrated *in vacuo*. ^{1}H NMR analysis showed 38% yield of quinone **15**. Flash silica gel chromatography (18% EtOAc in hexanes) afforded **15** (19.4 mg, 46%) as a red solid: mp = 90 ºC (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.48 (m, 1H), 7.44 – 7.37 (m, 5H), 7.35 – 7.28 (m, 5H), 7.23 (t, J = 7.4 Hz, 2H), 6.98 (m, 1H), 3.67 (s, 4H), 3.63 – 3.59 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.4, 180.5, 149.7, 138.8, 136.9, 135.3, 131.1, 130.3, 129.1, 128.7, 128.5, 127.2, 127.1, 124.3, 122.9, 112.9, 58.9, 51.0; IR (cm^{-1}) 3252, 3027, 2924, 1652, 1636, 1326; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{23}N_2O_2^+$ 407.1760, found 407.1753.

3-(((4-methoxybenzyl)(phenyl)amino)methyl)-1*H*-carbazole-1,4(9*H*)-dione (17). A 7 mL vial was charged with a magnetic stirring bar, quinone **9** (15 mg, 0.071 mmol, 1 equiv), N-PMB aniline (30.3 mg, 0.142 mmol, 2 equiv), closed and evacuated / backfilled with N_2 (3 cycles), then THF (0.75 mL), *i*-PrOH (0.25 mL) and Et_3N (99 μL, 0.71 mmol, 10 equiv) were added consecutively by syrinte. The reaction was stirred at rt for 8 h, then opened to air and stirred for an additional 3 h. The reaction was then concentrated *in vacuo* and flash silica gel chromatography (20% THF in hexanes) afforded **17** (10.8 mg, 36%) as a red solid: mp = 195-196 ºC; ^{1}H NMR (500 MHz, DMSO- d_6) δ 8.06 (dddd, J = 32.4, 8.0, 7.0, 1.2 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.40 (m, 1H), 7.33 (m, 1H), 7.19 (m, 2H), 7.12 (m, 2H), 6.89 (m, 2H), 6.62 (m, 1 H), 6.16 (t, J = 2.0 Hz, 1H), 4.60 (s, 2H), 4.54 (d, J = 2.0 Hz, 2H) 3.71 (s, 3H); ^{13}C NMR (126 MHz, DMSO- d_6) δ 183.2, 179.8, 158.2, 147.7, 146.8, 137.6, 135.9, 130.5, 129.4, 129.2, 128.0, 126.5, 124.1, 123.5, 121.7, 121.6, 116.4, 116.0, 114.0, 112.1, 55.1, 53.0, 49.3; IR (cm^{-1}) 3256, 2929, 1635, 1614, 1505, 1468; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{23}N_2O_3^+$ 423.1709, found 423.1703.

***tert*-butyl 3-methyl-1,4-dioxo-1,4-dihydro-9*H*-carbazole-9-carboxylate (19).** A 200 mL round bottom flask was charged with a magnetic stibar, quinone **9** (1 g, 4.73 mmol. 1 equiv), THF (80 mL), di-*tert*-butyl dicarbonate (1.34 g, 6.15 mmol, 1.3 equiv) and DMAP (57.8 mg, 0.472 mmol, 0.1 equiv) under air. The reaction mixture was stirred at room temperature and monitored by TLC. After 2 h the reaction was concentrated to about 20 mL and loaded into a neutral alumina column packed with 5% EtOAc in hexanes. The product was eluted with 5-10% EtOAc in hexanes. Compound **19** (1.41 g, 96%) was obtained as an orange solid: mp = 153–154 ºC (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dt, J = 7.9, 1.1 Hz, 1H), 8.01 (dt, J = 8.5, 1.0 Hz, 1H), 7.50 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.41 (ddd, J = 8.0, 7.2, 1.1 Hz, 1H), 6.54 (q, J = 1.6 Hz, 1H), 2.14 (d, J = 1.6 Hz, 3H), 1.67 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.5, 177.7, 148.6, 145.5, 138.32 135.4, 133.6, 128.5, 125.4, 123.6, 123.1, 121.6, 114.3, 86.0, 27.6, 15.4; IR (cm^{-1}) 2979, 1747, 1656, 1534, 1310, 1110; HRMS (ESI-TOF) *m/z* $[2M+Na]^+$ calcd for $C_{36}H_{34}N_2O_8Na^+$ 645.2213, found 645.2245.

***tert*-butyl 1,4-dihydroxy-3-(((4-methoxybenzyl)(phenyl)amino)methyl)-9*H*-carbazole-9-carboxylate (20a).** A dry 7 mL vial was charged with a magnetic stirbar, quinone **19** (104 mg, 0.334 mmol, 1 equiv) and N-PMB aniline (142 mg, 0.668 mmol, 2 equiv). The vial was capped and evacuated / backfilled with Ar (3 cycles). THF (0.7 mL) was added, followed by *i*-Pr_2NEt (0.7 mL). The vial was heated in an aluminum block at 65 ºC for 24 h. The reaction was cooled at room temperature, opened to air and concentrated *in vacuo*. Flash silica gel chromatography (10–15% EtOAc in hexanes) afforded **20a** (139.1 mg, 79%) as a light green solid. mp = 145 ºC (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 9.94 (s, 1H), 8.43 (m, 1H), 8.04

(m, 1H), 7.44 – 7.34 (m, 2H), 7.29 (m, 2H), 7.14 (m, 2H), 7.05 (m, 1H), 6.97 (d, J = 8.7 Hz, 1H), 6.79 (m, 3H), 4.35 (s, 2H), 4.31 (s, 2H), 3.77 (s, 3H), 1.77 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 154.2, 149.0, 146.1, 137.5, 137.4, 130.6, 129.1, 127.3, 126.4, 126.1, 125.8, 123.9, 123.50, 123.47, 122.0, 118.1, 116.6, 116.4, 116.0, 113.6, 86.5, 58.0, 55.1, 54.3, 28.3; IR (cm^{-1}) 3137, 2977, 1683, 1511, 1442; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{32}H_{33}N_2O_5^+$ 525.2384, found 525.2386.

***tert*-butyl 3-((allyl(phenyl)amino)methyl)-1,4-dihydroxy-9*H*-carbazole-9-carboxylate (20b).** A dry 7 mL vial was charged with a magnetic stirbar, quinone **19** (150 mg, 0.482 mmol, 1 equiv) and N-allyl aniline (0.13 mL, 0.964 mmol, 2 equiv). The vial was capped and evacuated / backfilled with Ar (3 cycles). THF (1 mL) was added, followed by *i*-Pr_2NEt (1 mL). The vial was heated in an aluminum block at 65 ºC for 12 h. The reaction was cooled at room temperature, opened to air and concentrated *in vacuo*. Flash silica gel chromatography (30–40% CH_2Cl_2 in hexanes) afforded **20b** (139.2 mg, 65%) containing ~9% of quinone **21b** as a yellowish foam. The mixture was submitted to the following step without further purification. Spectral data for **20b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.41 (s, 1H), 9.64 (s, 1H), 8.39 (d, J = 7.5 Hz, 1H), 8.06 – 7.99 (m, 1H), 7.42 – 7.27 (m, 4H), 7.20 (m, 2H), 7.03 (m, 1H), 6.77 (s, 1H), 5.83 (m, 1H), 5.25 – 5.12 (m, 2H), 4.46 (s, 2H), 3.87 (d, J = 6.5 Hz, 2H), 1.76 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 149.0, 146.0, 137.6, 137.6, 132.0, 129.2, 126.4, 126.2, 123.9, 123.6, 123.0, 120.6, 119.8, 118.2, 116.5, 116.0, 86.65, 56.3, 55.0, 28.3 (two carbon signals are missing due to overlap); IR (cm^{-1}) 3400, 3026, 2977, 1683, 1442, 1365; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{29}N_2O_4^+$ 445.2127, found 445.2119.

***tert*-butyl 1,4-dihydroxy-3-((methyl(phenyl)amino)methyl)-9*H*-carbazole-9-carboxylate (20c).** A dry 7 mL vial was charged with a magnetic stirbar, quinone **19** (150 mg, 0.482 mmol, 1 equiv) and N-methyl aniline (0.104 mL, 0.964 mmol, 2 equiv). The vial was capped and evacuated / backfilled with Ar (3 cycles). THF (1 mL) was added, followed by *i*-Pr_2NEt (1 mL). The vial was heated in an aluminum block at 65 ºC for 12 h. The reaction was cooled at room temperature, opened to air and 1,3,5-trimethoxybenzene (81.1 mg, 0.482 mmol, 1 equiv) was added, volatiles were removed *in vacuo* and the residue immediately analyzed by ^{1}H NMR. The crude reaction mixture contained 73% of hydroquinone **20c** and 10% of quinone **21c**. The mixture was submitted to oxidation without further purification. Selected signals from crude ^{1}H NMR (400 MHz, $CDCl_3$) 10.42 (s, 1H), 8.40 (m, 1H), 8.03 (m, 1H), 7.06 (m, 1H), 4.45 (s, 2H), 2.87 (s, 3H), 1.76 (s, 9H).

***tert*-butyl 3-(((4-methoxybenzyl)(phenyl)amino)methyl)-1,4-dioxo-1,4-dihydro-9*H*-carbazole-9-carboxylate (21a).** A 20 mL vial was charged with a magnetic stirbar, hydroquinone **20a** (286 mg, 0.545 mmol, 1 equiv) and MeCN (10 mL) and THF

(2 mL). Under air, a solution of $FeCl_3$ (884 mg, 3.27 mmol, 6 equiv) in 0.1 M HCl (6 mL) was added dropwise with vigorous stirring. The reaction was monitored by TLC. After ~15 min the reaction mixture was transferred to a separatory funnel rinsing with CH_2Cl_2 (15 mL) and washed with $NaHCO_{3\ (aq)}$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). Combined organic extracts were washed with water (5 mL), brine (5 mL), dried over $MgSO_4$, filtered through a short pad of silica gel and concentrated *in vacuo*. Compound **21a** (267 mg, 94%) was obtained as a brown foam: mp = 131 ºC (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (m, 1H), 8.02 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.51 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 7.23 – 7.14 (m, 3H), 6.86 (m, 2H), 6.77 – 6.67 (m, 3H), 6.49 (m, 1H), 4.60 (s, 2H), 4.53 (d, *J* = 2.1 Hz, 2H), 3.78 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.6, 177.5, 158.8, 148.5, 148.0, 143.9, 138.4, 135.3, 132.3, 129.7, 129.4, 128.7, 127.9, 125.5, 123.4, 123.0, 121.9, 117.3, 114.4, 114.2, 112.3, 86.2, 55.3, 53.9, 48.9, 27.6; IR (cm^{-1}) 2979, 1747, 1653, 1506, 1102; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{32}H_{30}N_2O_5Na^+$ 545.2052, found 545.2042.

***tert*-butyl 3-((allyl(phenyl)amino)methyl)-1,4-dioxo-1,4-dihydro-9*H*-carbazole-9-carboxylate (21b).** A 20 mL vial was charged with a magnetic stirbar, a 10:1 mixture of **20b** / **21b** (102 mg, ca. 0.229 mmol, 1 equiv) and MeCN (6 mL). Under air, Ag_2O (106 mg, 0.459 mmol, 2 equiv) was added with vigorous stirring. The reaction was monitored by ^{1}H NMR. After 90 min the reaction mixture was diluted with EtOAc, filtered through celite and concentrated *in vacuo* to afford **21b** (99 mg, 98%) as a light brown solid: mp = 105 ºC (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.03 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.52 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.21 (m, 2H), 6.74 (m, 1H), 6.67 (m, 2H), 6.49 (t, *J* = 2.1 Hz, 1H), 5.97 – 5.85 (m, 1H), 5.28 – 5.17 (m, 2H), 4.47 (d, *J* = 2.1 Hz, 2H), 4.02 (dt, *J* = 5.0, 1.7 Hz, 2H), 1.66 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.7, 177.5, 148.5, 147.7, 144.2, 138.4, 135.4, 132.9, 132.3, 129.3, 128.7, 125.5, 123.4, 123.0, 121.9, 117.3, 117.1, 114.4, 112.3, 86.2, 53.4, 48.9, 27.6. IR (cm^{-1}) 3960, 2979, 1747, 1653, 1504, 1109; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_4^+$ 443.1971, found 443.1982.

***tert*-butyl 3-((methyl(phenyl)amino)methyl)-1,4-dioxo-1,4-dihydro-9*H*-carbazole-9-carboxylate (21c).** A 20 mL vial was charged with a magnetic stirbar, a 7:1 mixture of **20c** / **21c** (268.7 mg, ca. 0.642 mmol, 1 equiv) and MeCN (10 mL). Under air, Ag_2O (297.8 mg, 1.285 mmol, 2 equiv) was added with vigorous stirring. The reaction was monitored by ^{1}H NMR. After 30 min the reaction mixture was diluted with EtOAc, filtered through celite and concentrated *in vacuo*. Flash silica gel chromatography (5% THF in hexanes) afforded **21c** (247 mg, 92%) as an orange solid: mp = 55 ºC (decomposition); ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.32 (dt, *J* = 7.9, 1.1 Hz, 1H), 8.02 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.52 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.25 (m, 2H), 6.79 – 6.69 (m, 3H), 6.46 (t, *J* = 2.1 Hz, 1H), 4.47 (d, *J* = 2.1 Hz, 2H), 3.09 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.7, 177.4, 148.4, 148.4, 144.1, 138.4, 135.3, 132.3, 129.3, 128.7, 125.5, 123.4, 123.0, 121.8, 117.3, 114.4, 112.1, 86.2, 51.3, 39.0, 27.5; IR (cm^{-1}) 2979, 1747, 1653, 1348, 1209, 1151; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_4^+$ 417.1814, found 417.1799.

***tert*-butyl 3-(((2-bromophenyl)(4-methoxybenzyl)amino)methyl)-1,4-dihydroxy-9*H*-carbazole-9-carboxylate (23).** A dry 7 mL vial was charged with a magnetic stirbar, quinone **19** (60 mg, 0.1927 mmol, 1 equiv) and 2-bromo-N-PMB aniline (112.6 mg, 0.3854 mmol, 2 equiv). The vial was capped and evacuated / backfilled with Ar (3 cycles). THF (0.4 mL) was added, followed by *i*-Pr_2NEt (0.4 mL). The vial was heated in an aluminum block at 65 ºC for 21 h. The reaction was cooled at room temperature, opened to air and 1,3,5-trimethoxybenzene (32.4, 0.1927 mmol, 1 equiv) was added. The mixture was concentrated *in vacuo* and analyzed by ^{1}H NMR. The crude contained 22% NMR yield of **23**. Flash silica gel chromatography (first column: 1:1 CH_2Cl_2 / hexanes, second column: 10% EtOAC in hexanes) afforded **23** (15 mg) as a tan solid: mp = 71 ºC (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 9.88 (s, 1H), 8.53 (m, 1H), 8.04 (m, 1H), 7.64 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.40 (m, 2H), 7.20 (m, 1H), 7.02 (td, *J* = 7.6, 1.5 Hz, 1H), 6.95 – 6.83 (m, 2H), 6.80 (m, 3H), 4.25 (s, 2H), 4.19 (s, 2H), 3.79 (s, 3H), 1.77 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 154.2, 146.9, 146.2, 137.5, 137.3, 133.7, 131.5, 127.8, 126.5, 126.4, 126.10, 126.01, 125.9, 125.1, 123.9, 123.8, 121.2, 117.3, 117.0, 116.5, 115.9, 113.4, 86.5, 56.0, 55.1, 54.1, 28.3; IR (cm^{-1}) 3143, 2979, 1683, 1440, 1364, 1208, 1146; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{32}H_{32}BrN_2O_5^+$ 603.1495, found 603.1484.

di-*tert*-butyl 6-hydroxy-15a-methyl-9,15-dioxo-8a,9,15,15a-tetrahydro-5*H*-pyrano[3,2-*b*:5,6-*c'*]dicarbazole-5,10(8*H*)-dicarboxylate (D1). A dry 7 mL vial was charged with a magnetic stirbar, quinone **19** (227 mg, 0.729 mmol, 1 equiv) and 2-bromo-N-PMB aniline (234 mg, 0.892 mmol, 1.1 equiv). The vial was capped and evacuated / backfilled with Ar (3 cycles). Dioxane (2.5 mL) was added, followed by *i*-Pr_2NEt (0.6 mL). The vial was heated in an aluminum block at 80 ºC for 12 h. The reaction was cooled at room temperature, opened to air and 1,3,5-trimethoxybenzene (40.8, 0.243 mmol, 0.33 equiv) was added. The mixture was concentrated *in vacuo* and immediately analyzed by ^{1}H NMR. The crude contained hydroquinone **23** (20%), dimer **D1** (18%) and unreacted **19** (9%) and undetermined byproducts. After exposure to air for 5 h, ^{1}H NMR analysis of this mixture showed a higher amount of unreacted **19** (39%). Flash silica gel chromatography (20-25% EtOAC in hexanes)

and trituration with MeCN afforded analytically pure **D1** (11 mg) as a yellow solid: mp = 160 ºC (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.37 (m, 1H), 8.29 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.07 (dt, *J* = 8.5, 0.9 Hz, 1H), 8.03 (dt, *J* = 8.6, 0.9 Hz, 1H), 7.54 (dddd, *J* = 20.0, 8.5, 7.2, 1.3 Hz, 1H), 7.44 – 7.32 (m, 3H), 6.72 (s, 1H), 3.61 (dd, *J* = 8.5, 6.6 Hz, 1H), 3.41 (ddd, *J* = 16.9, 8.6, 1.1 Hz, 1H), 3.18 (ddd, *J* = 16.8, 6.6, 0.9 Hz, 1H), 1.86 (s, 3H), 1.75 (s, 9H), 1.67 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.5, 187.8, 154.1, 148.1, 141.1, 139.1, 138.9, 138.4, 137.6, 129.1, 126.5, 125.7, 125.7, 125.4, 124.1, 123.7, 123.6, 123.6, 121.7, 116.9, 116.0, 115.7, 115.0, 114.5, 86.7, 86.3, 82.4, 54.7, 28.3, 27.5, 25.2, 23.9; IR (cm^{-1}) 3140, 2979, 2933, 1732, 1688, 1445, 1079; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{36}H_{34}N_2O_8Na^+$ 645.2213, found 645.2241.

***tert*-butyl 3-(((2-bromophenyl)(4-methoxybenzyl)amino)methyl)-1,4-dioxo-1,4-dihydro-9*H*-carbazole-9-carboxylate (24).** A 7 mL vial was charged with a magnetic stirring bar, **23** (27 mg, 0.0448 mmol, 1 equiv), MeCN (1.5 mL) and Ag_2O (20.7 mg, 0.0895 mmol, 2 equiv). The resulting suspension was stirred vigorously and the reaction monitored by TLC. After 1.5 h the mixture was diluted with CH_2Cl_2 (2 mL) and filtered through a short pad of celite / silica gel, rinsing with CH_2Cl_2. The filtrate was concentrated *in vacuo* to afford **24** (26 mg, 97%) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.23 (m, 1H), 7.98 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.62 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.39 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.29 (m, 2H), 7.18 (ddd, *J* = 8.0, 7.2, 1.5 Hz, 1H), 7.06 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.94 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1H), 6.84 – 6.79 (m, 3H), 4.19 (s, 2H), 4.16 (d, *J* = 2.4 Hz, 1H), 3.75 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.2, 177.7, 158.9, 148.5, 148.3, 144.8, 138.3, 135.2, 134.1, 134.0, 129.9, 129.4, 128.5, 128.0, 125.5, 125.4, 123.9, 123.5, 123.0, 121.7, 121.5, 114.3, 113.8, 86.1, 58.3, 55.2, 48.5, 27.6; IR (cm^{-1}) 2978, 2931, 1747, 1652, 1511, 1098; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{32}H_{29}BrN_2O_5Na^+$ 623.1158, found 623.1161.

***tert*-butyl 1'-(4-methoxybenzyl)-1,4-dioxo-1,4-dihydrospiro[carbazole-3,3'-indoline]-9(2*H*)-carboxylate (25).** A 7 mL vial was charged with a magnetic stirring bar, **24** (10 mg, 0.01663 mmol, 1 equiv), K_2CO_3 (9.2 mg, 0.665 mmol. 4 equiv) and $Pd(PPh_3)_4$ (19.2 mg, 0.01663 mmol, 1 equiv). The vial was closed and evacuated / backfilled with Ar (3 cycles), then dioxane (0.5 mL) was added by syringe. The reaction mixture was heated in an aluminum block at 80 ºC for 4 h. The reaction was then cooled at rt, opened to air and filtered through celite, rinsing with EtOAc. Flash silica gel chromatography (10-30% EtOAc in hexanes) afforded **25** (5.2 mg, 60%) as a yellowish film: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.07 (dt, *J* = 8.6, 0.9 Hz, 1H), 7.55 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.10 (td, *J* = 7.7, 1.3 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.75 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.54 (td, *J* = 7.5, 1.0 Hz, 1H),

4.39 (d, J = 14.6 Hz, 1H), 4.24 (d, J = 14.6 Hz, 1H), 4.10 (d, J = 9.4 Hz, 1H), 3.81 (s, 3H), 3.34 – 3.20 (m, 3H), 1.66 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.1, 186.6, 158.7, 151.3, 148.3, 139.5, 138.6, 130.0, 129.5, 129.4, 129.1, 129.0, 125.4, 125.3, 123.9, 123.7, 123.4, 117.9, 114.3, 114.0, 108.0, 86.2, 60.8, 59.6, 55.3, 52.0, 51.2, 27.6; IR (cm^{-1}) 2924, 1750, 1683, 1511, 1370; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{32}H_{31}N_2O_5^+$ 523.2233, found 523.2227.

***tert*-butyl 2-bromo-3-methyl-1,4-dioxo-1,4-dihydro-9*H*-carbazole-9-carboxylate (26).** A dry 100 mL round bottom flask was charged with a magnetic stirring bar, quinone **19** (1.4 g, 4.5 mmol, 1 equiv) and dichloromethane (40 mL) under air, the solution was cooled in an ice bath and bromine (0.25 mL, 4.95 mmol, 1.1 equiv) was added drowpise. The cold bath was removed and the reaction stirred at room temperature. After 1 h full conversion of **19** was determined by ^{1}H NMR analysis of an aliquot. Then sodium acetate (1.1 g, 13.5 mmol. 3 equiv) was added, followed by dry DMSO (5 mL). The suspension was stirred at room temperature overnight (~18 h). ^{1}H NMR analysis of the reaction mixture indicated complete conversion of the intermediate bromide to **26**. The reaction was diluted with dichloromethane (50 mL) and washed with water (2 x 20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated. Column chromatography on silica (10% EtOAc in hexanes, then EtOAc / CH_2Cl_2 / hexanes 1:4:5) afforded 1.65 g (94%) of **26** as an orange solid: mp = 198 ºC (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (dt, J = 8.0, 1.1 Hz, 1H), 8.02 (dt, J = 8.5, 0.9 Hz, 1H), 7.53 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.43 (ddd, J = 8.1, 7.2, 1.0 Hz, 1H), 2.32 (s, 3H), 1.68 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.6, 170.5, 148.3, 145.3, 138.8, 135.9, 134.1, 129.1, 125.7, 123.4, 123.3, 121.6, 114.4, 86.5, 27.5, 16.9; IR (cm^{-1}) 2978, 2933, 1750, 1677, 1656, 1259, 1112; HRMS (ESI-TOF) *m/z* [M-Boc-H]$^-$ calcd for $C_{13}H_7BrNO_2^-$ 287.9660, found 287.9677.

***tert*-butyl 2-bromo-1,4-dihydroxy-3-(((4-methoxybenzyl)(phenyl)amino)methyl)-9*H*-carbazole-9-carboxylate (27).** A 7 mL vial was charged with a magnetic stirring bar, quinone **26** (40 mg, 0.1025 mmol, 1 equiv), N-PMB aniline (32.8 mg, 0.1538 mmol, 1.5 equiv) and CH_2Cl_2 (0.4 mL). The vial was capped, flushed with Ar (balloon), and *i*-Pr_2Net (3.6 μL, 0.0205 mmol, 0.2 equiv) was added. The reaction was stirred at room temperature. After 4.5 h the reaction was concentrated *in vacuo*. Flash silica gel chromatography (10-15% THF in hexanes) afforded **27** (55.4 mg, 90%) as a light yellow foam: mp = 86 ºC (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.30 (s, 1H), 11.26 (d, J = 0.8 Hz, 1H), 8.41 (m, 1H), 7.99 (m, 1H), 7.44 – 7.31 (m, 2H), 7.31 – 7.26 (m, 3H), 7.18 (m, 2H), 7.08 – 7.02 (m, 3H), 6.83 – 6.79 (m, 2H), 4.67 (s, 2H), 4.29 (s, 2H), 3.77 (s, 3H), 1.74 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 154.3, 148.5, 146.4, 137.5, 135.1, 130.8, 129.2, 127.3, 126.4, 126.0,

125.8, 124.3, 124.1, 123.7, 122.4, 117.0, 116.0, 115.5, 113.8, 112.0, 87.1, 59.7, 55.2, 55.1, 28.2; IR (cm^{-1}) 3350, 3057, 2977, 1680, 1610, 1435, 1150; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{32}H_{32}BrN_2O_5^+$ 603.1495, found 603.1497.

***tert*-butyl 2-bromo-3-(((4-methoxybenzyl)(phenyl)amino)methyl)-1,4-dioxo-1,4-dihydro-9*H*-carbazole-9-carboxylate (28).** A 20 mL vial was charged with a magnetic stirbar, hydroquinone **27** (688 mg, 1.14 mmol, 1 equiv) and MeCN (25 mL). Under air, a solution of $FeCl_3$ (924 mg, 3.42, 3 equiv) in 0.1 M HCl (10 mL) was added dropwise with vigorous stirring. The reaction was monitored by TLC. After ~30 min the reaction mixture was transferred to a separatory funnel rinsing with CH_2Cl_2 (50 mL) and washed with $NaHCO_{3\,(aq)}$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). Combined organic extracts were washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was recrystallized from dry THF to give **28** (604 mg, 88%) as a dark green solid: mp = 156 ºC (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.0 Hz, 1H), 8.01 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.51 (ddd, *J* = 8.5, 7.1, 1.3 Hz, 1H), 7.41 (td, *J* = 7.6, 7.1, 1.0 Hz, 1H), 7.26 (m, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.2, 2H) 6.81 (t, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 2H), 4.65 (s, 2H), 4.56 (s, 2H), 3.41 (s, 3H), 1.68 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.1, 170.1, 158.3, 149.9, 148.1, 144.5, 138.8, 137.7, 133.8, 131.3, 129.2, 129.1, 128.3, 125.6, 123.3, 121.8, 118.3, 114.6, 114.4, 113.7, 86.3, 55.5, 54.8, 49.9, 27.5; IR (cm^{-1}) 3058, 2980, 2932, 1748, 1676, 1536, 1108; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{32}H_{30}BrN_2O_5^+$ 601.1338, found 601.1349.

(9-(*tert*-butoxycarbonyl)-3-(((4-methoxybenzyl)(phenyl)amino)methyl)-1,4-dioxo-4,9-dihydro-1*H*-carbazol-2-yl)bis(triphenylphosphane)palladium(II) bromide (29): A 7 mL vial was charged with a magnetic stirring bar, **28** (35 mg, 0.0582 mmol, 1 equiv), $Pd(PPh_3)_4$ (67.2 mg, 0.0582 mmol, 1 equiv). The vial was sealed and evacuated / backfilled with Ar (3 cycles), then toluene (1.5 mL) was added by syringe. The reaction was heated in an aluminum block at 80 ºC. After 3 h the reaction was cooled to room temperature, opened to air and concentrated *in vacuo*. Flash silica gel chromatography (25-30% EtOAc in hexanes) afforded **28** (68 mg, 95%) as a dark brown solid. X-ray quality crystals were grown from a MeCN solution at room temperature overnight. mp = 153 ºC (decomposition); Note: two species are observed in solution by ^{1}H NMR and ^{31}P NMR, whose ratio is concentration dependent. Major species: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.80 (m, 1H), 7.90 – 7.51 (m, 12H), 7.40 (ddd, *J* = 8.5, 7.1, 1.3 Hz, 1H), 7.30 (m, 1H), 7.20 (m, 18H), 7.09 (dd, *J* = 8.8, 7.2 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.72 – 6.65 (m, 3H), 6.59 (m, 2H), 4.57 (s, 2H), 4.49 (s, 2H), 3.74 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.1 (t, *J* = 2.7 Hz), 180.4, 179.9, 158.0, 149.1, 148.9, 145.3 (t, *J* = 4.2 Hz), 137.4, 135.0, 134.4, 130.9 (t, *J* =

23.7 Hz), 130.7, 130.3, 128.8, 128.0 (t, J = 5.2 Hz), 127.8, 127.6, 124.4, 123.3, 123.1, 120.6, 116.8, 114.2, 113.64, 113.61, 85.1, 55.2, 54.6, 53.5, 27.4; $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) δ 20.9 (major species), 21.2 (minor species); IR (cm^{-1}) 3054, 1742, 1635, 1505, 1368, 1349, 1100; HRMS (ESI-TOF) *m/z* $[M+MeCN–Br]^+$ calcd for $C_{70}H_{62}N_3O_5P_2Pd^+$ 1192.3199, found 1192.3157.

***tert*-butyl 2-bromo-1,4-dihydroxy-3-(((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)methyl)-9*H*-carbazole-9-carboxylate (33).** A dry 50 mL round bottom flask was charged with a magnetic stirbar, quinone **26** (1.28 g, 3.278 mmol, 1 equiv), aniline **31** (790 mg, 3.605 mmol, 1.1 equiv) and CH_2Cl_2 (11 mL). The flask was capped and flushed with Ar (balloon). Then, *i*-Pr_2NEt (114 μL, 0.656, 0.2 equiv) was added by syringe. After 9 h, the flask was opened to air, diluted with CH_2Cl_2 (60 mL) and washed with 0.1 M $HCl_{(aq)}$ (5 mL). The organic phase was washed $NaHCO_{3\,(aq)}$, dried over $MgSO_4$ and concentrated. The mixture was triturated with EtOAc / hexanes to afford 1.288 g of **33** as a tan solid. The remaining solution was concentrated, triturated again with EtOAc / hexanes to afford 59 mg of **33**. Overall yield: 67%. mp = 150 ºC (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.32 (s, 1H), 10.64 (s, 1H), 8.39 (d, J = 7.7 Hz, 1H), 8.02 (dt, J = 8.4, 0.9 Hz, 1H), 7.74 (dd, J = 7.4, 1.7 Hz, 1H), 7.39 (m, 1H), 7.33 (m, 2H), 6.93 (m, 1H), 6.87 (s, 1H), 4.87 (s, 2H), 1.77 (s, 9H), 1.37 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3, 154.0, 146.4, 137.5, 136.8, 135.3, 133.3, 126.4, 126.1, 125.6, 124.1, 123.7, 120.1, 117.7, 116.0, 115.9, 114.2, 111.1, 87.2, 84.1, 50.8, 28.2, 24.9; ^{11}B (128 MHz, $CDCl_3$) δ 32.1; IR (cm^{-1}) 3351, 2976, 1681, 1371, 1207, 1150, 913, 747; HRMS (ESI-TOF) *m/z* $[M+H^+$ calcd for $C_{30}H_{35}BBrN_2O_6^+$ 609.1772, found 609.1767.

***tert*-butyl 2-bromo-1,4-dihydroxy-3-(((4-methoxybenzyl)(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)methyl)-9*H*-carbazole-9-carboxylate (32) and oxidation to *tert*-butyl 2-bromo-3-(((4-methoxybenzyl)(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)methyl)-1,4-dioxo-1,4-dihydro-9*H*-carbazole-9-carboxylate (34).** A dry 7 mL vial was charged with a magnetic stirbar, quinone **26** (100 mg, 0.256 mmol, 1 equiv), aniline **30** (95.6 mg, 0.282 mmol, 1.1 equiv) and CH_2Cl_2 (0.85 mL). The vial was capped and flushed with Ar (balloon). Then, *i*-Pr_2NEt (9 μL, 0.0513, 0.2 equiv) was added by syringe. After 5 h, the vial was opened to air and CH_2Cl_2 (2 mL) was added, followed by 1,3,5-trimethoxybenzene (43.1 mg, 0.256 mmol, 1 equiv). ^{1}H NMR analysis indicated 72% NMR yield of **32**. Attempts to purify it were unsuccessful, but its structure was partially supported by the following data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2 (s, 1H), 10.99 (s, 1H), 8.47 (d, J = 7.6 Hz, 1H), 7.99 (m, overlapped, 1H), 7.84 (m, 1H), 6.99 (m, 2H), 6.77 (m, overlapped, 2H), 4.53 (s, 2H), 4.24 (s, 2H), 1.73 (s, 9H), 1.47(s, 12H); The crude was submitted to oxidation: the crude was concentrated *in*

vacuo and dissolved in MeCN (3 mL) and EtOAc (4 mL). Ag_2O (118.8 mg, 0.513 mmol, 2 equiv based on initial **26**) was added and the mixture stirred vigorously. After 5 h the reaction was filtered through a plug of celite, rinsing with THF and the filtrate concentrated *in vacuo*. ^{1}H NMR analysis indicated 27% NMR yield of **34**. Attempts to purify **34** by conventional means were not successful, however, product **34** estimated to be >70% pure was obtained by slow precipitation at 0º C (2 weeks) from the crude reaction mixture dissolved in EtOAc / hexanes. A black solid that was collected by filtration, washed with hexanes and dried: mp = 127–128 ºC (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dt, *J* = 7.9, 1.2 Hz, 1H), 8.02 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.71 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.51 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.41 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.35 (ddd, *J* = 8.1, 7.2, 1.8 Hz, 1H), 7.29 (m, 2H), 7.19 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.02 (td, *J* = 7.3, 1.0 Hz, 1H), 6.60 (m, *J* = 8.6 Hz, 2H), 4.48 (s, 2H), 4.33 (s, 2H), 3.51 (s, 3H), 1.68 (s, 9H), 1.29 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.3, 170.8, 158.5, 157.5, 148.3, 144.5, 138.8, 137.0, 136.6, 134.0, 131.5, 131.4, 130.1, 128.9, 125.4, 123.5, 123.4, 123.2, 122.2, 121.8, 114.3, 113.2, 86.2, 83.5, 59.3, 54.9, 51.5, 27.5, 24.9; ^{11}B (128 MHz, $CDCl_3$) δ 33.3; IR (cm^{-1}) 2977, 2932, 1749, 1675, 1608, 1350; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{38}H_{41}BBrN_2O_7^+$ 727.2190, found 727.2209.

***tert*-butyl 2-bromo-1,4-dioxo-3-(((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)methyl)-1,4-dihydro-9*H*-carbazole-9-carboxylate (35).** A 7 mL vial was charged with a magnetic stirring bar, **33** (78 mg, 0.128 mmol, 1 equiv), acetonitrile (3 mL) and EtOAc (2 mL). Under vigorous stirring, Ag_2O (59 mg, 0.256 mmol, 2 equiv) was added and the reaction monitored by TLC. After 15 min the reaction was filtered through a short plug a celite and silica gel, rinsing with THF, to afford **35** (74 mg, 95%) as a dark green solid: mp = 161–162 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.01 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.60 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.52 (ddd, *J* = 8.5, 7.1, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.31 (ddd, *J* = 8.7, 7.2, 1.8 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.70 – 6.58 (m, 2H), 4.58 (d, *J* = 7.1 Hz, 2H), 1.67 (s, 9H), 1.34 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.5, 170.5, 153.3, 148.2, 145.1, 139.0, 137.5, 137.2, 134.0, 133.2, 129.3, 125.7, 123.4, 123.3, 121.7, 116.4, 114.5, 110.4, 86.5, 83.7, 41.8, 27.6, 24.9; ^{11}B (128 MHz, $CDCl_3$) δ 31.7; IR (cm^{-1}) 3350, 2977, 1653, 1636, 1435, 1354; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{30}H_{33}BBrN_2O_6^+$ 607.1615, found 607.1615.

Calothrixin B (1). A Schlenk flask was charged with a magnetic stirring bar, **35** (1.02 g, 1.68 mmol, 1 equiv), $(dppf)PdCl_2{\cdot}CH_2Cl_2$ (68.6 mg, 0.084 mmol, 0.05 equiv) and K_2CO_3 (1.16 g, 8.4 mmol, 5 equiv). The flask was closed with septum and evacuated / backfilled with Ar (4 cycles), then dioxane (50 mL) and degassed H_2O (10 mL) were added by syringe. The reaction was heated in an oil bath at 100 ºC with vigorous stirring. After 5.5 h the reaction was cooled to room temperature,

opened to air and transferred to a separatory funnel, rinsing with THF (200 mL), EtOAc (110 mL) and H_2O (50 mL). The aqueous phase was extracted with ~1:1 THF/EtOAc (2 x 50). The combined organic extracts were washed with H_2O (2 x 50 mL), brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash silica gel chromatography (10-20% THF in hexanes) afforded **1** (397.3 mg, 79%) as a red solid: mp > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 9.57 (s, 1H), 9.53 (dd, J = 8.6, 1.5 Hz, 1H), 8.13 (d, J = 7.9 Hz, 2H), 7.91 (ddd, J = 8.4, 6.7, 1.5 Hz, 1H), 7.85 (ddd, J = 8.4, 6.8, 1.5 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.42 (m, 1H), 7.35 (t, J = 7.5 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 180.9, 180.3, 151.2, 147.5, 138.5, 138.1, 132.6, 131.6, 130.2, 129.8, 127.20, 127.12, 124.9, 124.3, 123.4, 122.6, 122.3, 115.5, 114.0; HRMS (ESI-TOF) *m/z* [M-H]$^-$ calcd for $C_{19}H_9N_2O_2^-$ 297.0664, found 297.0662. The spectral data is in accordance with published values.[1]

Calothrixin A (2). Compound **2** was prepared according to a published procedure.[3a] 20 mL round bottom flask was charged with a magnetic stirring bar, compound **1** (4 mg, 0.013 mmol, 1 equiv) and *m*-CPBA (~77% w/w, 17 mg, 0.0671, ~5 equiv) and CH_2Cl_2 (6 mL). A reflux condenser was attached, the system was flushed with Ar and the reaction refluxed for 4 h. The reaction was then cooled at room temperature, diluted with CH_2Cl_2 (50 mL) and extracted with $NaHCO_{3\,(sat)}$ (3 x 10 mL) and water, until *p*H was neutral. The solution was dried over Na_2SO_4, and concentrated *in vacuo*. Flash silica gel chromatography (1% Et_3N in CH_2Cl_2) afforded **2** (2.4 mg, 57%) as an orange solid: mp = 288–290 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.2 (s, 2H), 9.67 (m, 1H), 8.87 (s, 1H), 8.60 (m, 1H), 8.11 (d, J = 7.9 Hz, 2H), 8.03 – 7.93 (m, 2H), 7.59 (dt, J = 8.3, 1.0 Hz, 2H), 7.44 (ddd, J = 8.3, 7.1, 1.3 Hz, 2H), 7.37 (ddd, J = 8.0, 7.0, 1.1 Hz, 2H); ^{13}C NMR (126 MHz, DMSO) δ 178.3, 177.8, 143.1, 138.7, 138.1, 132.0, 131.9, 131.8, 129.9, 128.2, 127.0, 126.9, 124.5, 123.4, 122.0, 121.9, 119.1, 115.1, 114.0; HRMS (ESI-TOF) *m/z* [M-H]$^-$ calcd for $C_{19}H_9N_2O_3^-$ 313.0613, found 313.0610. The spectral data is in accordance with published values.[1]

ASSOCIATED CONTENT

Supporting Information

The supporting information if available free of charge on the ACS Publications website. Copies of ^{1}H, ^{13}C, ^{11}B and ^{31}P NMR spectra of isolated compounds and crystallographic data for compounds **28** and **29**.

AUTHOR INFORMATION

Corresponding Author

*email: mclift@ku.edu

ORCID

Michael D. Clift: 0000-0001-6441-9802

Luis M. Mori-Quiroz: 0000-0001-8546-7264

ACKNOWLEDGMENTS

We thank Prof. Mercy Anyika and Mr. Andrew Rider (Metropolitan Community College – Penn Valley, MO) for the preparation of compound **5**; and Dr. Victor Day (KU) for crystallographic analysis. Financial support from the University of Kansas and is gratefully acknowledged. Support for NMR instrumentation used in this study was provided by NIH Shared Instrumentation Grants # S10RR024664 and # S10OD016360, and NSF Major Instrumentation Grant # 0320648.

REFERENCES

1. Rickards, R. W.; Rothschild, J. M.; Willis, A. C.; de Chazal, N. M.; Kirk, J.; Kirk, K.; Saliba, K. J.; Smith, G. D. *Tetrahedron*, **1999**, *55*, 13513–13520.
2. Doan, N. T.; Stewart, P. R.; Smith, G. D. *FEMS Microbiol. Lett.* **2001**, *196*, 135–139.
3. Representative examples (for a complete list see the supporting information) (a) Kelly, T. R.; Zhao, Y.; Cavero, M.; Torneiro, M. *Org. Lett.* **2000**, *2*, 3735–3737. (b) Bernardo, P. H.; Chai, C. L. L.; Elix, J. A. *Tetrahedron Lett.* **2002**, *43*, 2939–2940. (c) Tohyama, S.; Choshi, T.; Matsumoto, K.; Yamabuki, A.; Ikegata, K.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett.* **2005**, *46*, 5263–5264. (d) Lee, S.; Kim, K.-H.; Cheon, C.-H. *Org. Lett.* **2017**, *19*, 2785–2788.
4. Mori-Quiroz, L. M.; Clift, M. D. *Org. Lett.* **2016**, *18*, 3446–3449.
5. (a) Smith, L. I.; Dobrovolny, F. J. *J. Am. Chem. Soc.* **1926**, *48*, 1693−1709. (b) Smith, L. I.; Webster, I. M. *J. Am. Chem. Soc.* **1937**, *59*, 662−667. (c) Smith, L. I.; Tenenbaum, D. *J. Am. Chem. Soc.* **1937**, *59*, 667−672.
6. For the earlier reports on alkylquinone amination see: (a) Cameron, D. W.; Scott, P. M.; Todd, L. *J. Chem. Soc.* **1964**, 42−48. (b) Cameron, D. W.; Giles, R. G. F.; Titman, R. B. *J. Chem. Soc.* **1969**, 1245−1251. (c) Jurd, L. *Aus. J. Chem.* **1978**, *31*, 347–352. (d) Kallmayer, H.-J. *Arch. Pharm.* **1979**, *312*, 73–75. (e) Kallmayer, H.-J. *Arch. Pharm.* **1979**, *312*, 230–239. (f) Chakraborty, M.; McConville, D. B.; Niu, Y.; Tessier, C. A.; Youngs, W. J. *J. Org. Chem.* **1998**, *63*, 7563–7567.
7. For examples of alkylquinone thiolation see: (a) King, T. J.; Thomson, R. H.; Worthington, R. D. *J. Chem. Soc. Chem. Comm.* **1980**, 777–778. (b) Thomson, R. H.; Worthington, R. D. *J. Chem. Soc. Perkin Trans. I,* **1980**, 282–288. (c) Thomson, R. H.; Worthington, R. D. *J. Chem. Soc. Perkin Trans. I,* **1980**, 289–292.
8. Lin, C.; Du, H.-J.; Zhao, H.; Yan, D.-F.; Liu, N.-X.; Sun, H.; Wen, X.; Xu, Q.-L. *Org. Biomol. Chem.* **2017**, *15*, 3472–3478.

9. (a) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron*, **2002**, *58*, 5367–5405. (b) Bai, W.-J.; David, J. G.; Feng, Z.-G.; Weaver, M. G.; Wu, K.-L.; Pettus, T. R. R. *Acc. Chem. Res.* **2014**, *47*, 3655–3664. (c) Singh, M. S.; Nagaraju, A.; Anand, N.; Chowdhury, S. *RSC Adv.* **2014**, *4*, 55924–55959.
10. Huang, Y.; Zhang, J.; Pettus, T. R. R. *Org. Lett.* **2005**, *7*, 5841–5844.
11. (a) Lumb, J.-P.; Trauner, D. *Org. Lett.* **2005**, *7*, 5865–5868. (b) Volgraf, M.; Lumb, J.-P.; Brastianos, H. C.; Carr, G.; Chung, M. K. W.; Münzel, M.; Mauk, A. G.; Andersen, R. J.; Trauner, D. *Nat. Chem. Biol.* **2008**, *4*, 535–537.
12. Lumb, J.-P.; Choong, K. C.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 9230–9231.
13. Furukawa, H.; Wu, T.-S.; Ohta, T.; Kuoh, C.-S. *Chem. Pharm. Bull.* **1985**, *33*, 4132–4138.
14. (a) Yogo, M.; Ito, C.; Furukawa, H. *Chem. Pharm. Bull.* **1991**, *39*, 328–334. (b) Hagelin, H.; Oslob, J. D.; Åkermark, B. *Chem. Eur. J.* **1999**, *5*, 2413–2416.
15. (a) Åkermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. *J. Org. Chem.* **1975**, *40*, 1365–1367. (b) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022–5028. (c) Guo, D.-D.; Li, B.; Wang, D.-Y.; Gao, Y.-R.; Guo, S.-H.; Pan, G.-F.; Wang, Y.-Q. *Org. Lett.* **2017**, *19*, 798–801. (d) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787–8863.
16. (a) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2–3. (b) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186–9187. (c) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578–7584. (d) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590.
17. Up to 18% NMR yield of dimer **D1** was obtained when the reaction was run in dioxane at 80 ºC.
18. (a) Smith, L. I.; Tess, R. W. H.; Ullyot, G. E. *J. Am. Chem. Soc.* **1944**, *66*, 1320–1323. (b) Lapidot, A.; Silver, B. L.; Samuel, D. *J. Biol. Chem.* **1996**, *241*, 5537–5541. (c) Giraud, L.; Giraud, A. *Synthesis*, **1998**, 1153–1160.
19. Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447–471.
20. Analysis of the reaction mixture showed rapid formation of N-Boc protected calothrixin B, which then underwent hydrolysis to give **1**.