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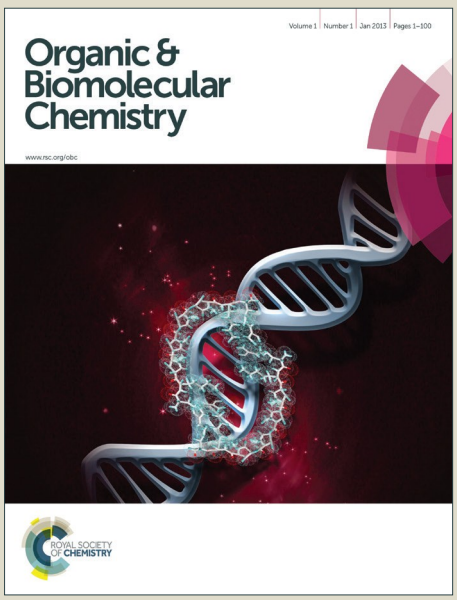

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Synthesis of carbazoloquinone natural products 'on-water'

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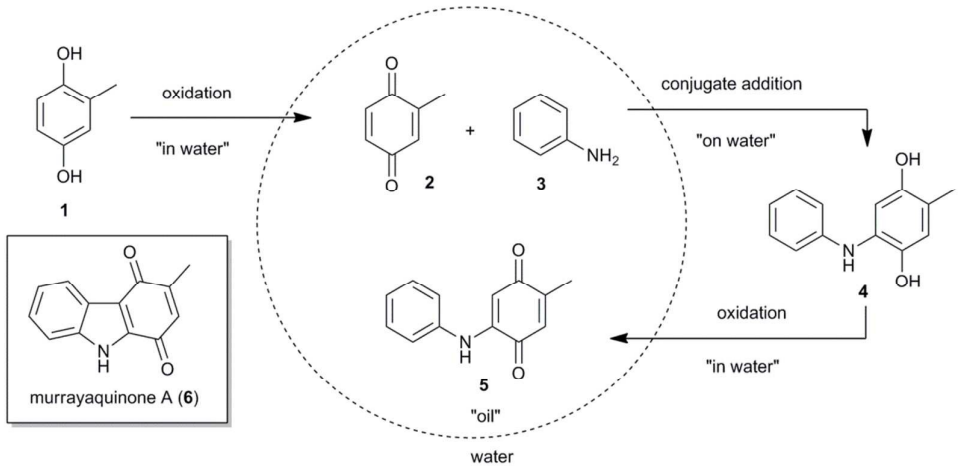
The total synthesis of a number of carbazolo-1,4-quinone natural products using on-water chemistry is described. A recently developed domino 'in-water, on-water' process is employed to rapidly and efficiently generate königinequinone A, which subsequently enables access to murrayaquinones B, C, D and E, and pyrayaquinones B and C, via a remarkably facile on-water catalysed Claisen rearrangement.

Introduction

Despite a growing appreciation of the need to promote environmentally sustainable processes within the synthetic organic chemistry community, the use of water as the sole reaction medium remains underutilised.[1] The advantages of water, namely its non-toxicity, non-flammability, abundance, low cost and high heat capacity, have often been outweighed by the perceived disadvantage of its inability to solvate most organic compounds. Increasingly, however, on-water processes – in which reactions involving water-insoluble substrates are conducted as aqueous emulsions – have emerged as exciting ways to harness the potential of water for organic synthesis.[2-4] Aqueous insolubility is a strict requirement for on-water chemistry as it is the enhanced acidity of interfacial water molecules that catalyses the organic reaction inside the emulsion droplet.[5, 6] As such, on-water reactions exhibit rate enhancements compared to the same reactions occurring in either organic solvents or in the absence of solvents (i.e. under neat conditions). Aside from elucidating the mechanism underlying on-water catalysis,[5] we have invented novel processes for the use of on-water reactions in conjunction with traditional in-water reactions in one-pot, domino sequences (Scheme 1).[7, 8] For our recent total synthesis of the naturally occurring carbazoloquinone alkaloid murrayaquinone A (**6**) (Scheme 1), we coupled an in-water oxidation reaction with an on-water catalysed aniline conjugate addition reaction.[7] In that instance, the different aqueous solubility of compounds **1–5** caused them to be shuttled into or out of emulsion droplets, allowing the in-water and on-water reactions to occur in the same vessel.

Herein we report the total synthesis of carbazoloquinone

Scheme 1 In-water, on-water domino process as the key step in the synthesis of murrayaquinone A (**6**).



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natural products containing substituted aromatic rings using an in-water, on-water domino process. During these synthetic endeavours we have investigated the effect that different oxidants have on the domino process and uncovered a pair of remarkably facile on-water catalysed aromatic Claisen rearrangements.

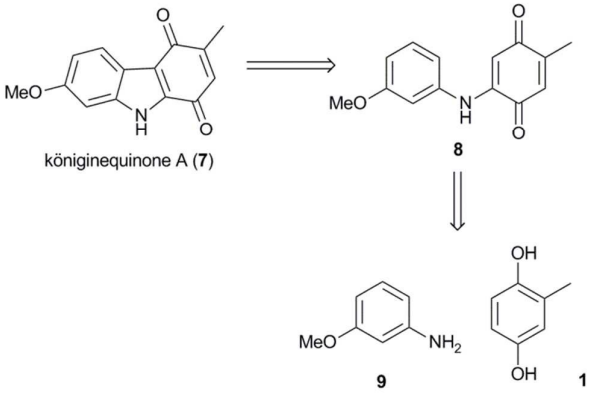
Results and discussion

Synthesis of königinequinone A

Our initial synthetic target was the methoxyl containing carbazoloquinone, königinequinone A (**7**) (Scheme 2) which was isolated in low yield (0.0015%) from the stem bark of the curry tree, *Murraya königii* Spreng.[9] Whilst extracts of the curry tree are reported to exhibit a plethora of biological effects,[10] no specific biological activity has yet been attributed to königinequinone A (**7**). Kapil and co-worker achieved a total synthesis of königinequinone A (**7**) before its status as a natural product was known.[11] Since then, königinequinone A (**7**) has been synthesised on three occasions. Chowdhury and Saha employed a Japp-Klingemann indole synthesis followed by Fremy's salt oxidation,[9] an approach that was later improved by Saha using an immobilised CAN oxidation.[12] The most direct synthesis of königinequinone A (**7**) was reported by Knölker and co-worker who employed a palladium-mediated oxidative coupling,[13] a reaction subsequently put to use in our own synthesis.

As outlined in Scheme 2, disconnection of the central C-C bond of the carbazole unit revealed compound **8**. Conversion of **8** into **7** is known.[13] We anticipated that compound **8** could be produced using our in-water oxidation, on-water conjugate addition domino sequence. We have previously assessed the compatibility of electron-rich anilines with the domino process and were confident that the planned union was feasible.[7] We therefore anticipated a two-step total synthesis of königinequinone A (**7**) starting from *m*-anisidine (**9**) and toluhydroquinone (**1**).

Scheme 2 Retrosynthetic analysis of königinequinone A (**7**).



In analogy with our previous work, oxidative conditions developed by Minisci and co-workers featured as the in-water component of the domino process.[7, 14] As such, toluhydroquinone (**1**) was dissolved in aqueous hydrogen peroxide. *m*-Anisidine (**9**) and a catalytic amount of iodine (10 mol-%) were added and the mixture was vigorously stirred to generate an emulsion (Scheme 3). As shown in Table 1, after only 10 minutes at room temperature an acceptable yield of the desired conjugate addition product **8** (41%) was obtained, along with the easily separable minor regioisomer **10** (31%) (entry 1). In the absence of vigorous stirring, no emulsion formed and none of the conjugate addition product was observed (entry 2). Since the in-water and on-water components of the domino process are completely independent of each other and occur in different phases of the emulsion (see Scheme 1), there is no inherent reason why the in-water reaction is restricted to the Minisci oxidation. We anticipated that other commonly used, water-soluble oxidants could be employed in the process with equal facility. In this way, the catalytic iodine used in the Minisci protocol could be substituted with catalytic silver (I) oxide to give **8** and **10** in comparable yields (Table 1, entry 3). In our previous studies we found that some electron-rich compounds underwent undesired reactions with aqueous hydrogen peroxide.[7] It was therefore gratifying to see that the in-water oxidation could be carried out with sodium periodate (entry 4), which has the advantage of being easily weighed, allowing for strict control of oxidant stoichiometry. The use of ceric ammonium nitrate

Scheme 3 In-water, on-water synthesis of **8**.

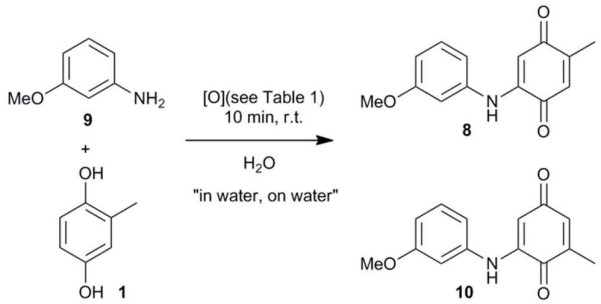
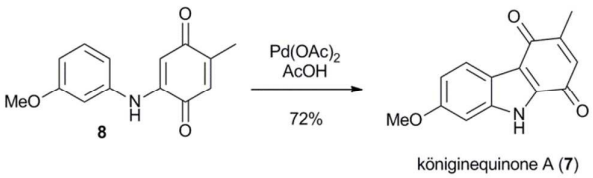


Table 1 Effect of oxidant on the in-water, on-water domino process.

Entry	Oxidant [a]	Yield (%) [b]	Ratio **8**:**10** [c]
1	aq. H_2O_2, I_2, (10 mol%)	72	1.3:1
2	aq. H_2O_2, I_2, (10 mol%) [d]	0	-
3	aq. H_2O_2, Ag_2O, (10 mol%)	71	1.4:1
4	$NaIO_4$	59	1.4:1
5	$(NH_4)_2Ce(NO_3)_6$	37	1.3:1
6	$KMnO_4$	decomp.	-
7	Oxone®	decomp.	-
8	$KBrO_3$	n.r. [e]	-

[a] Reaction time 10 min. at room temperature. [b] Isolated yield after chromatography. [c] determined by ^{1}H NMR analysis of the crude mixture. [d] Reaction mixture stirred at 250 rpm. [e] No reaction.



Scheme 4 Synthesis of königinequinone A (**7**).

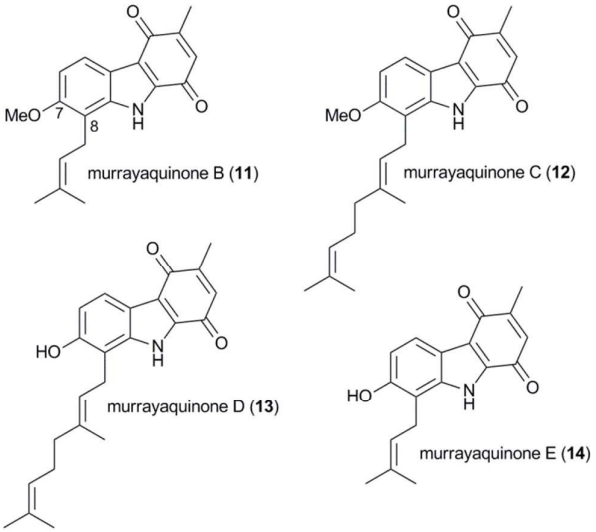
also gave the desired products, albeit in reduced yield (entry 5). The use of stronger oxidants such as potassium permanganate and potassium peroxymonosulfate (Oxone®) led to product decomposition (entries 6 and 7). Surprisingly, potassium bromate failed to promote the in-water reaction (entry 8).

The two step synthesis of königinequinone A (**7**) was completed by treating compound **8** with palladium acetate under refluxing acetic acid, according to the method of Knölker[13] (Scheme **4**). These reaction conditions favoured formation of the desired regioisomer (*d.r* 3.5:1) which could be separated by chromatography.

Synthesis of murrayaquinones B, C, D and E

Having employed the in-water, on-water domino process for the synthesis of a methoxy-substituted carbazoloquinone natural product, our attention turned to other members of the family (Figure 1). Murrayaquinones B–E (**11**–**14**), isolated from *Murraya euchrestifolia*, feature either a hydroxy or methoxy group at the C7 position, along with either a prenyl or geranyl group at the C8 position.[15, 16] The isolation of murrayaquinone B (**11**) represented the first report of a naturally occurring carbazoloquinone. Perhaps because it displayed only marginal activity against leukaemia in a tumour cell-line assay,[17] murrayaquinone B has not been a popular synthetic target, with only two syntheses reported to date. Moody and co-worker developed a one-pot Claisen rearrangement – Hemetsberger indole synthesis *en route* to the natural product.[18, 19] Kapil and co-worker utilised a PCC oxidation of naturally occurring murrayafoline B.[20, 21] As yet, there are no reports detailing total syntheses of the remaining murrayaquinones C–E (**12**–**14**) or pyrayaquinone C (**27**).

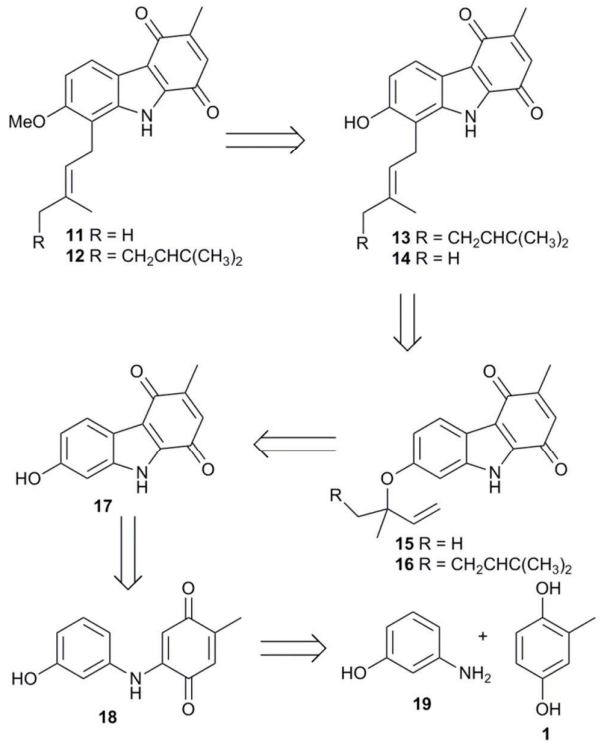
Fig. 1 Structures of murrayaquinones B–E.

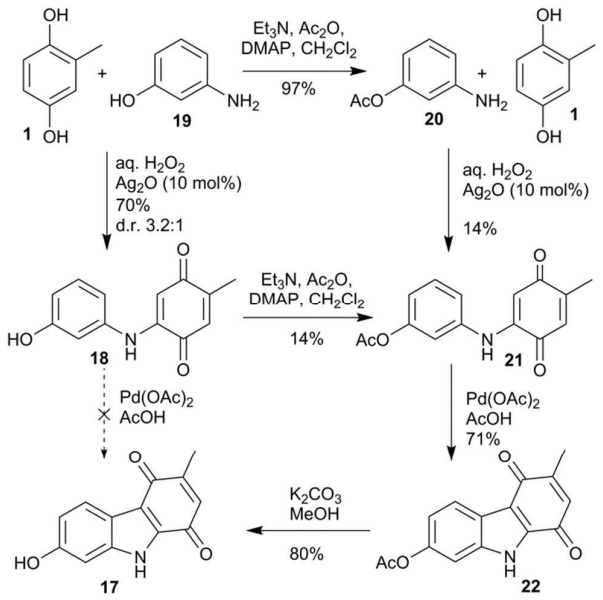


As depicted in Scheme 5, we envisaged a divergent approach to the murrayaquinones. Methylation would give murrayaquinones B (**11**) and C (**12**) from murrayaquinones E (**14**) and D (**13**) respectively. Installation of the unsaturated side-chains of **13** and **14** was anticipated to result from regioselective, on-water catalysed Claisen rearrangements.[8] The substrates for these rearrangements, **15** and **16**, would be the product of selective *O*-alkylation of 7-hydroxy-3-methylcarbazoloquinone (**17**), obtained by ring-closure of **18**. Compound **18** would in turn be produced from *m*-aminophenol (**19**) and toluhydroquinone (**1**) using the in-water, on-water domino process. This approach posed two challenges: the selective in-water oxidation of **1** in the presence of the relatively electron-rich **19**, and the palladium-mediated ring-closure of the unprotected phenol **18**.

Pleasingly, the in-water, on-water domino reaction involving *m*-aminophenol (**19**) and toluhydroquinone (**1**) proceeded satisfactorily, favouring the desired regioisomer **18** (Scheme 6). However, despite extensive efforts, we were unable to perform the palladium-catalysed transformation of compound **18** into the key intermediate **17**. Given that the methoxy-substituted derivative readily participated in the cyclisation (see Scheme 4) this unexpected result was attributed to the presence of the free phenol. Attempts to circumvent the issue by masking the phenol unit of **18** as an acetate proved to be equally troublesome due to the

Scheme 5 Retrosynthetic analysis of murrayaquinones B–E (**11**–**14**).



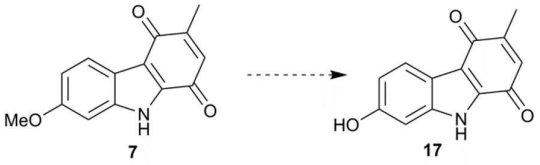


Scheme 6 Synthesis of key intermediate **17**.

competing reactivity of the quinone unit as a Michael acceptor and the heightened lability of the hydrogens on the C3 methyl group. Switching the order of those two synthetic operations did not improve matters. Selective *O*-acetylation of aminophenol **19** proceeded in near quantitative yield, but unacceptably low yields were obtained when **20** was subjected to the in-water, on-water domino process. As an aside, the acetate unit of **20** proved to be labile under these reaction conditions, which is in good agreement with our proposal that on-water catalysis results from acid-catalysis at the oil–water interface of an emulsion.[5] Our inability to produce **21** in appreciable quantities was disappointing, particularly when coupled with the fact that treatment of **21** with palladium acetate and removal of the acetate unit gave the desired **17** in good yield and moderate regioselectivity.

Dissatisfied with this initial synthetic route our attention turned to a more scalable alternative. Having established the efficient synthesis of königinequinone A (**7**) using in-water, on-water domino chemistry (*vide supra*), it was envisioned that a simple demethylation would deliver the key intermediate **17** required for the synthesis of murrayaquinones B-E (**11**–**14**). As such, compound **7** was subjected to a range of standard demethylation protocols (Table 2). Frustratingly, these were either completely ineffective or caused material decomposition.

As with the seemingly trivial acetylation of compound **18**, it became apparent that the competing reactivity of the quinone moiety was frustrating our synthetic efforts. Rather than coordination to the ethereal oxygen followed by nucleophilic substitution at the methyl group, we suspected that the demethylating reagents may be preferentially activating the quinone oxygen toward nucleophilic addition reactions, leading to decomposition pathways. In order to suppress this conflicting reactivity, we elected to temporarily remove the



Entry	Reagent	Temp. (°C)	Time (h)	Yield (%)[a]
1	BBr_3	0–20	2	decomp.
2	$AlCl_3$	20–40	20	n.r.[c]
3	$AlCl_3$, TBAB[b]	40	4	n.r.[c]
4	LiCl	153	18	decomp.
5	pyridine·HCl	250	0.5	decomp.
6	HBr (48% in H_2O), TBAB	100	0.5	n.r.[c]
7	HBr (33% in AcOH)	117	4	decomp.

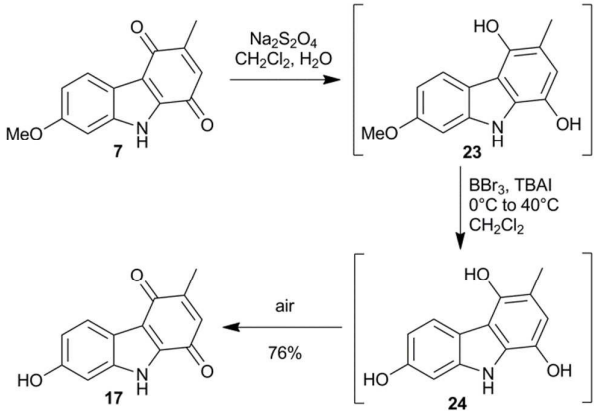
[a] Isolated yield after chromatography. [b] TBAB = tetrabutylammonium bromide. [c] No reaction.

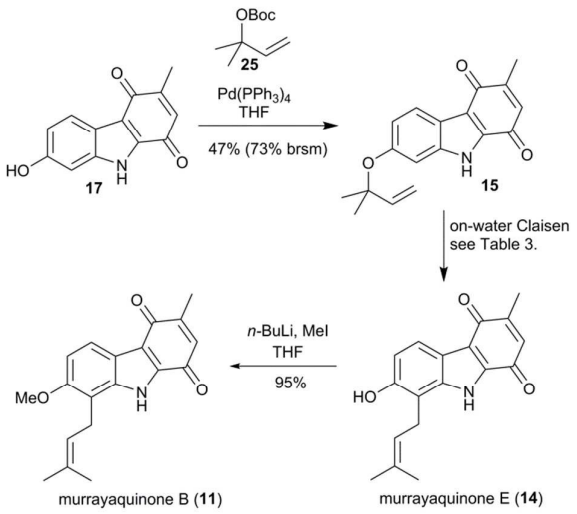
Table 2 Attempted demethylation of königinequinone A (**7**).

quinone unit (Scheme 7). As such, compound **7** was reduced to the dihydroquinone **23** with sodium dithionite, which was immediately treated with boron tribromide and tetrabutylammonium iodide at 0°C to give the desired phenol product **17** in acceptable yield. Presumably, aerobic oxidation of the electron-rich intermediate **24** occurs spontaneously upon reaction workup.

With compound **17** in hand, we were able to proceed to the first total synthesis of murrayaquinone E (**14**) (Scheme 8). Chemoselective *O*-allylation of **17** with carbonate **25** in the presence of tetrakis(triphenylphosphine)palladium gave compound **15** in moderate yield. While attempts to improve this reaction by using other palladium sources and Buchwald-type ligands met with no success, the unreacted phenol **17** could be recycled, allowing for material throughput. Synthesis of **15** set the scene for the anticipated regioselective Claisen rearrangement. As detailed in Table 3, stirring compound **15** on-water at 50°C led to 29% conversion into the natural product **14** after 24 hours (entry 1). When the on-water reaction was conducted at 80°C, complete conversion was

Scheme 7 Improved synthesis of key intermediate **17**





Scheme 8 Synthesis of murrayaquinones B and E.

observed (entry 2), with **14** being isolated in 92% yield after chromatography. In contrast, when a solution of **15** in toluene was heated at 80°C for 24 hours, only a trace amount of the product **14** was observed (entry 3). Heating **15** under neat conditions at 80°C for 24 hours resulted in just 19% conversion (entry 4). Confirmation that the rate acceleration observed for this Claisen rearrangement was due to an on-water effect rather than a solvent polarity effect was ascertained by conducting the reaction in methanol under reflux (entry 5). This led to only 13% conversion over the same reaction time – less than half the conversion obtained on-water under less forcing conditions (compare entries 1 and 5). The Claisen rearrangement was completely regioselective with only the desired regioisomer of the product **14** being detected.

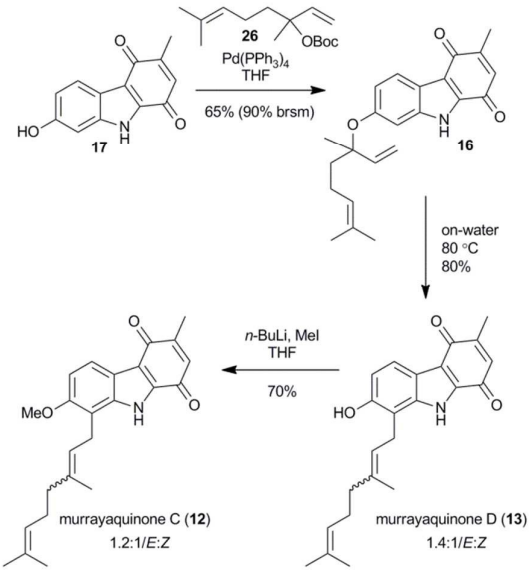
Thus the first reported total synthesis of murrayaquinone E (**14**) was completed in 5 steps from inexpensive and readily available starting materials using our recently devised in-water, on-water domino methodology coupled with a facile on-water catalysed Claisen rearrangement as the key bond-forming steps (Scheme 8). Straightforward alkylation of **14** with methyl iodide gave murrayaquinone B (**11**) in high yield, in just one additional step.

The total synthesis of murrayaquinone D (**13**) followed an analogous route (Scheme 9). Selective *O*-alkylation of the common intermediate **17** using the (±)-linalyl carbonate **26** and tetrakis(triphenylphosphine)palladium gave compound **16**. Due to the presence of a more complex side-chain, we were interested in a study of the regio- and diastereoselectivity of

Table 3 On-water Claisen rearrangement of **15**.

Entry	Solvent	Temp. (°C)	Conversion (%)[a,b]
1	on-H_2O	50	29
2	on-H_2O	80	100 (92)[c]
3	toluene	80	-
4	neat	80	19
5	MeOH	65	13

[a] Reaction time 24 h. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Isolated yield after chromatography.



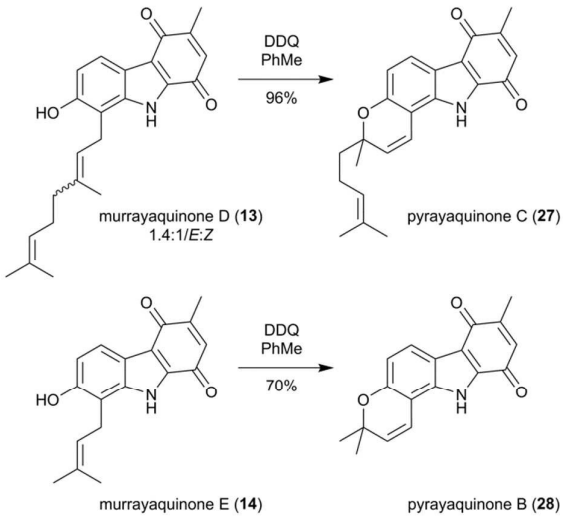
Scheme 9 Synthesis of murrayaquinones C and D.

the subsequent Claisen rearrangement under the on-water conditions. We were pleased to observe complete regioselectivity for the conversion of **16** into murrayaquinone D (**13**) which was collected in 80% yield after chromatography, albeit as an inseparable mixture of diastereomers (*E*:*Z*, 1.4:1). All attempts to isomerise this mixture to give predominately the *E*-configured isomer were ultimately unsuccessful. Alkylation of **14** with methyl iodide was straightforward and completed the synthesis of murrayaquinone C (**12**).

Synthesis of pyrayaquinones B and C

Pyrayaquinones C (**27**) and B (**28**) (Scheme 10) were isolated from the same natural source as the murrayaquinones and feature a related architecture in which the geranyl and prenyl units have cyclised to give the 6-membered rings.[22, 23] Ramesh and Kapil reported a synthesis of pyrayaquinone B (**28**) that features a DDQ oxidation,[11] while Furukawa and co-workers utilised a palladium-mediated oxidative coupling to access

Scheme 10 Synthesis of pyrayaquinones C (**27**) and B (**28**).



compound **28**.[24] In contrast, pyrayaquinone C (**27**) has not previously been synthesised.

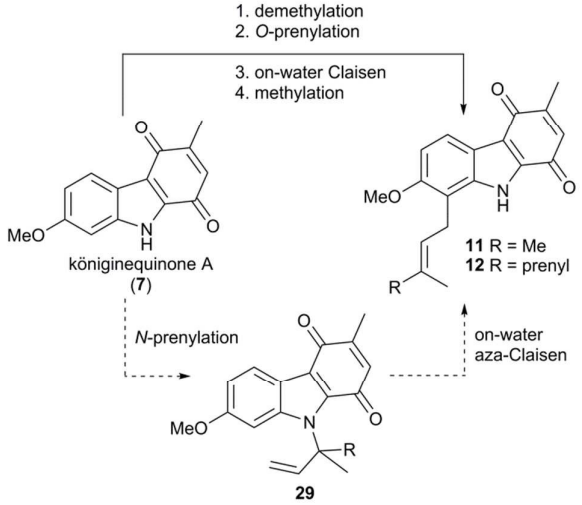
In this instance, treatment of murrayaquinone D (**13**) (obtained from the on-water Claisen rearrangement) with DDQ led to cyclisation occurring in excellent yield and completed the first total synthesis of pyrayaquinone C (**27**). Similarly, murrayaquinone E (**14**) was cyclised to give pyrayaquinone B (**28**) under the same reaction conditions (Scheme 10).

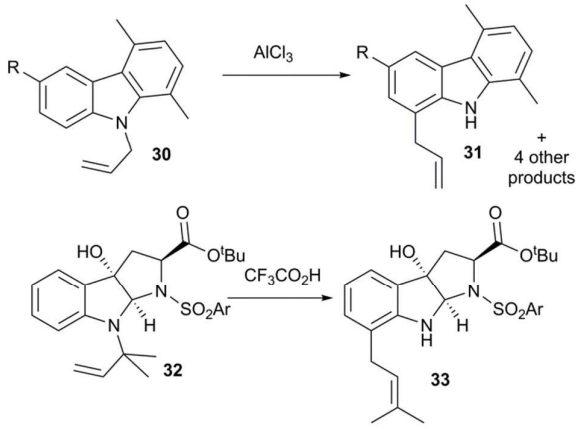
Attempted aromatic aza-Claisen rearrangement

Although we were able to access murrayaquinones B, C, D and E, and pyrayaquinones B and C in either 5 or 6 steps from very simple starting materials, the step-economy of the sequence held potential for further optimisation (Scheme 11). Given that königinequinone A (**7**) was demethylated to provide access to murrayaquinone E (**14**) only to have the deleted methyl group reinstated to provide murrayaquinone B (**11**), we envisioned a more ambitious synthetic strategy. Rather than an on-water catalysed Claisen rearrangement from the C7 oxygen to introduce the unsaturated group onto C8, an on-water catalysed aza-Claisen rearrangement from the carbazole nitrogen of compound **29** could be used to install the unsaturated side-chain, circumventing the need to tamper with the existing methyl ether.

Whilst there are no examples of aza-Claisen rearrangements from the nitrogen atom of carbazoloquinone structures of the type we proposed (**29** → **11**), related work instilled some confidence in the proposed transformation. There is a solitary report which details aza-Claisen rearrangements from the nitrogen atom of carbazole structures (Scheme 12). Sainsbury and co-workers effected the Lewis acid-catalysed rearrangement of **30** into **31**, however, that reaction also produced other compounds including chlorinated and dimeric products.[25] Nonetheless, it suggested that despite being conjugated with two aromatic ring systems, the nitrogen lone pair could still undergo protonation and charge-accelerated rearrangement. Disrupting conjugation resulted in an increase in the rate of rearrangement. Ganesan

Scheme 11 Revised retrosynthetic analysis of murrayaquinone B (**11**).



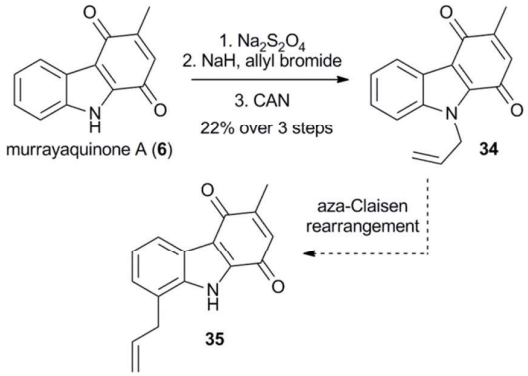


Scheme 12 Related aza-Claisen rearrangements.

and co-workers reported that the rearrangement of the hexahydro[2,3-*b*]pyrroloindole **32** was catalysed by trifluoroacetic acid and gave **33** in excellent yield at room temperature.[26] Additionally, our laboratory has recently reported that the aromatic aza-Claisen rearrangement of reverse *N*-prenylated naphthylamines and anilines is catalysed on-water.[6]

To test the validity of the aromatic aza-Claisen approach, we elected to study the rearrangement of the model compound *N*-allyl-murrayaquinone A (**34**). As shown in Scheme 13, to overcome competing *O*-alkylation the quinone unit of murrayaquinone A (**6**) was reduced with sodium dithionite, the intermediate was per-allylated and finally, oxidation with cerium ammonium nitrate gave the required substrate **34** in unoptimised yields. When **34** was then subjected to on-water reaction conditions at 80 °C (Table 4, entry 2) no rearranged product was observed, even after prolonged reaction times. Raising the temperature of the emulsion above the boiling point of water in a sealed tube (entry 4) failed to facilitate the rearrangement. Suspecting that the nitrogen atom of the carbazoloquinone was simply not basic enough to be protonated by interfacial water, we attempted the acid-catalysed rearrangement with trifluoroacetic acid (entry 5). Even though that reagent has a

Scheme 13 Unoptimised synthesis of *N*-allyl murrayaquinone A (**34**).



Entry	Solvent	Temp. (°C)	Time (h)	Conversion (%)[a]
1	neat	80	48	-
2	on-H_2O	80	48	-
3	neat	150[b]	36	-
4	on-H_2O	150[b]	36	-
5	TFA in CH_2Cl_2[c]	r.t.	18	-
6	$Et_2NC_6H_5$	216	8	decomp.

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] Sealed tube. [c] 10 mol-% TFA.

Table 4 Attempted Claisen rearrangement of **34**.

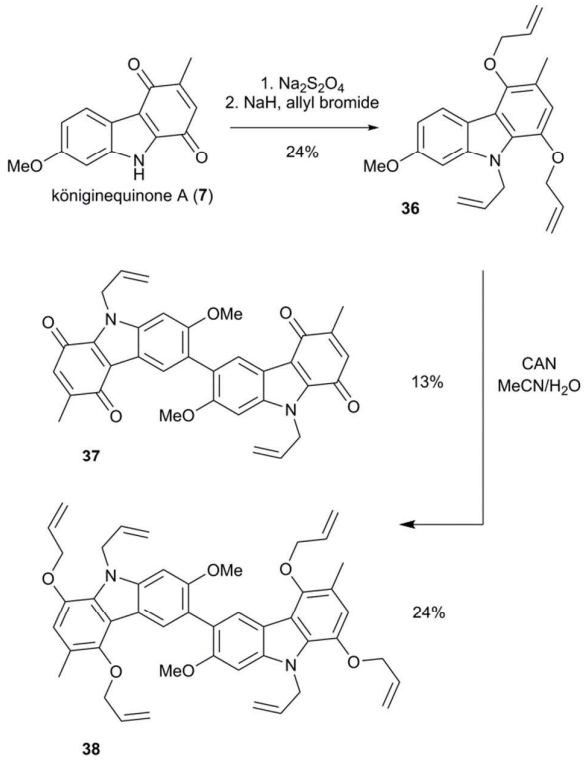
pK_a of 2.5, it failed to initiate the charge-accelerated process, demonstrating the lack of reactivity of the carbazole nitrogen.

Of course, the corresponding reverse *N*-prenylated königinequinone A (**29**) that would be required for the total synthesis of murrayaquinone B (see Scheme 11) would not only benefit from the Thorpe-Ingold effect of the gem-dimethyl group, but would contain a more electron-rich aromatic ring, rendering the corresponding carbazole nitrogen more nucleophilic. Testing the combination of these effects proved to be more challenging than anticipated.

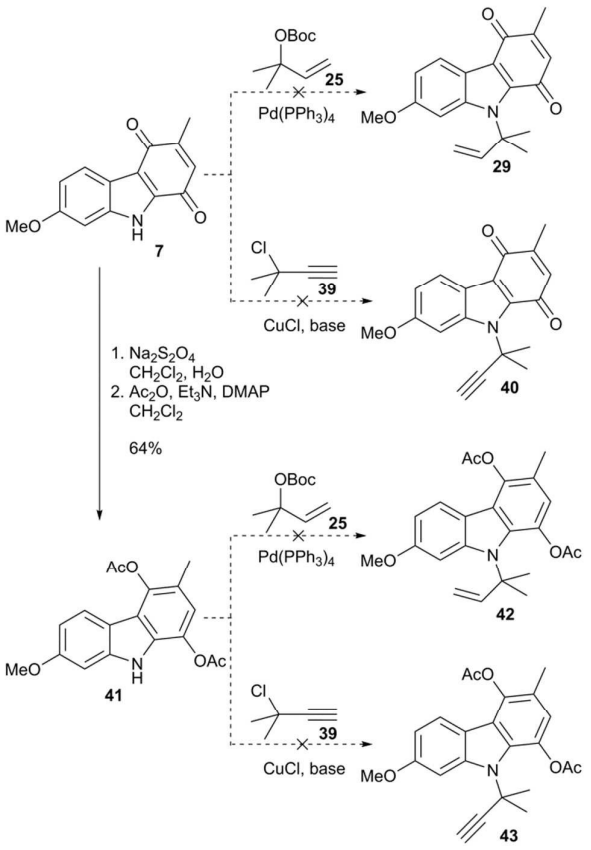
To examine the latter of these hypotheses, that of the assisting electron-rich aromatic ring, königinequinone A (**7**) was subjected to a reduction/perallylation/oxidation sequence analogous to that of murrayaquinone A (**6**) (Scheme 13). Intriguingly, the action of ceric ammonium nitrate on compound (**36**) facilitated a dehydrogenative homo-coupling to give compounds (**37**) and (**38**) (Scheme 14). Dimeric carbazole natural products are commonly isolated alongside their corresponding monomers.[27] However, only one dimeric carbazoloquinone has been reported to date, bismurrayaquinone A, in which the murrayaquinone A (**6**) subunits are coupled at the C2 site of the quinone.[28] Conducting the ceric ammonium nitrate oxidation under more dilute conditions served only to decrease the rate of this reaction to favour isolation of compound (**38**).

At this stage we revised our approach towards an aza-Claisen substrate in favour of a direct reverse prenylation reaction. In our previous work we had generated reverse *N*-prenylated anilines using a straightforward palladium-catalysed coupling.[6] As such, königinequinone A (**7**) was treated with carbonate **25** in the presence of tetrakis(triphenylphosphine)palladium (Scheme 15). However, even at elevated temperatures, no alkylation product **29** was observed. The more traditional approach to reverse *N*-prenylated substrates involves coupling with a propargylic chloride followed by chemoselective hydrogenation.[29] Unfortunately, treatment of **7** with 3-chloro-3-methylbut-1-yne (**39**) in the presence of copper(I) chloride and di*iso*propylethylamine did not lead to the anticipated product **40**. Applying more strongly basic conditions for the reaction (**7** → **40**) including the use of aqueous sodium hydroxide under phase transfer conditions and potassium *tert*-butoxide in dimethyl sulfoxide, led only to decomposition. Again, we

Scheme 14 Unexpected dimerization of **36**.



Scheme 15 Attempted reverse *N*-prenylation reactions.



reasoned that the enamine character of the anilinoquinone **7** was hindering our progress. Given that Sainsbury and co-workers could allylate a carbazole nitrogen to generate **30** (see Scheme 12) and given our previous recourse to a carbazole intermediate for both the successful demethylation of königinequinone A (**7**) (see Scheme 7) and the allylation of murrayaquinone A (**6**) (see Scheme 13), we were hopeful that reduction of the quinone unit of **7** to the corresponding dihydroquinone may allow synthetic access to the desired compound **29**.

As depicted in Scheme 15, the reductive acetylation of königinequinone A (**7**) proceeded in good yield to give compound **41**. With the competing phenol units masked as methoxy or acetyl groups, we were confident that the carbazole nitrogen of **41** would be the most reactive centre in the molecule.

Disappointingly, and despite extensive experimentation, this compound also resisted our efforts at *N*-alkylation under palladium or copper catalysis. Our inability to generate this key aza-Claisen precursor **29** directly from königinequinone A (**7**) denied us the opportunity to test our hypothesis regarding the enhanced likelihood of a charge-accelerated Claisen rearrangement. It is pertinent to note that we are unable to locate any literature examples of unsubstituted carbazoloquinones undergoing *N*-allylation.[30, 31] Our inability to transform **7** into **29** in a single step meant that the aza-Claisen strategy (set down in Scheme 11) was untenable.

Conclusions

We have completed the synthesis of a number of carbazoloquinone natural products using our recently developed domino in-water, on-water methodology as the key step. By employing an in-water oxidation with an on-water conjugate addition process, followed by a palladium-mediated ring closure, königinequinone A (**7**) was synthesized in just 2 steps. During that work we demonstrated that the in-water component of the domino process was not restricted to a particular oxidant, but was tolerant of a variety of reagents. Demethylation of **7** provided a common intermediate **17** for the synthesis of several other natural products. The application of an on-water catalysed aromatic Claisen rearrangement allowed us to complete the first total syntheses of murrayaquinones D and E (**13** and **14**) in just 5 steps respectively. Methylation of (**13** and **14**) under standard conditions completed the syntheses of murrayaquinones B and C (**11** and **12**) in just 6 steps. Finally, oxidative cyclisation of murrayaquinones D and E (**13** and **14**) gave pyrayaquinones C (**27**) and B (**28**) respectively.

We anticipate that this in-water, on-water domino approach will be suitable for many other carbazoloquinone natural products and their analogues. Although we could not translate it directly to the carbazole aza-Claisen rearrangement in this instance, we anticipate that this operationally simple in-water, on-water process will be compatible with a broad range of chemical transformations. Such research continues in our laboratory and will be reported in due course.

Acknowledgements

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Experimental

2-(3-Methoxyanilino)-5-methyl-1,4-benzoquinone (8) and 2-(3-methoxyanilino)-6-methyl-1,4-benzoquinone (10). *m*-Anisidine (1.30 mL, 11.6 mmol) and toluhydroquinone (2.16 g, 17.4 mmol) were taken up in water (30 mL). Silver(I) oxide (404 mg, 1.74 mmol) was added and the reaction mixture was stirred vigorously for 5 minutes. With a gas outlet attached, aqueous hydrogen peroxide solution (30% v/v, 5 mL) was added gradually over 20 minutes with continued vigorous stirring. Brine (50 mL) was added and the mixture extracted with dichloromethane (4 × 100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel, eluting with 10% ethyl acetate in light petroleum, gave compound **8** (1.20 g, 43%) as a dark purple solid; R_f = 0.23 (10% ethyl acetate in light petroleum); mp 112–113 °C (lit.[32] mp 110–112 °C); λ_{max} (MeOH)/nm 501 (ε 5520); ν_{max} (solid)/cm^{-1} 3302, 1668, 1639, 1579, 1259, 1207, 1037; δ_H (300 MHz; $CDCl_3$) 7.31-7.28 (2 H, m, ArH + NH), 6.81-6.70 (3 H, m, ArH), 6.56 (1 H, q, *J* = 1.0 Hz), 6.21 (1 H, s), 3.81 (3 H, s, OCH_3), 2.09 (3 H, d, *J* = 0.9 Hz, CH_3); δ_C (75 MHz; $CDCl_3$) 186.8 (C), 183.8 (C), 160.6 (C), 149.7 (C), 142.9 (C), 138.8 (C), 130.5 (CH), 129.4 (CH), 114.3 (CH), 110.7 (CH), 108.0 (CH), 101.4 (CH), 55.5 (CH_3), 16.5 (CH_3); *m/z* (APCI) 244 (MH^+, 100%), 213 (20); and compound **10** (622 mg, 22%) as a dark purple solid; R_f = 0.16 (10% ethyl acetate in light petroleum); mp 96-98 °C (lit.[27] mp 96-98 °C); λ_{max} (MeOH)/nm 500 (ε 3990); ν_{max} (solid)/cm^{-1} 3284, 1645, 1574, 1487, 1335, 1229, 1151, 1036; δ_H (300 MHz; $CDCl_3$) 7.31-7.26 (2 H, m, ArH + NH), 6.81-6.71 (3 H, m, ArH), 6.52 (1 H, s), 6.17 (1 H, m), 3.82 (3 H, s, OCH_3), 2.08 (3 H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 187.0 (C), 184.6 (C), 160.7 (C), 143.0 (C), 141.4 (C), 138.9 (C), 136.1 (CH), 130.5 (CH), 114.5 (CH), 110.9 (CH), 108.2 (CH), 101.4 (CH), 55.5 (CH_3), 15.6 (CH_3); *m/z* (APCI) 244 (MH^+, 100%), 213 (19).

Königinequinone A (7).[32] Compound **8** (250 mg, 1.03 mmol) and palladium(II) acetate (230 mg, 1.03 mmol) in glacial acetic acid (25 mL) were heated under reflux for 4.5 hours under an inert atmosphere. The mixture was then filtered through a pad of Celite™, the filtrate was extracted with diethyl ether (3 × 100 mL), washed with water (3 × 100 mL) and saturated aqueous sodium hydrogencarbonate solution (100 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. Flash chromatography on silica gel, eluting with dichloromethane, gave compound **7** (178 mg, 72%) as a 3.5:1 regioisomeric mixture; a dark brown solid; R_f = 0.18 (dichloromethane); mp 225–226 °C (decomp.) (lit.[32] mp 236–238 °C decomp.); λ_{max} (MeOH)/nm 398 (ε 3920); ν_{max} (solid)/cm^{-1} 3205, 1632, 1603, 1535, 1436, 1379, 1271, 1162, 1035; δ_H (300 MHz; DMSO-d_6) 7.85 (1 H, d, *J* = 8.7 Hz), 6.94-

6.88 (2 H, m), 6.50 (1 H, d, *J* = 1.2 Hz), 3.80 (3 H, s), 2.01 (3 H, d, *J* = 1.2 Hz); δ_C (75 MHz; DMSO-d_6) 183.2 (C), 179.4 (C), 158.8 (C), 147.1 (C), 138.9 (C), 135.0 (C), 131.6 (CH), 122.4 (CH), 117.7 (C), 115.9 (C), 115.1 (CH), 95.1 (CH), 55.3 (CH_3), 15.5 (CH_3); *m/z* (APCI) 242 (MH^+, 100%), 229 (31).

2-(3-Hydroxyanilino)-5-methyl-1,4-benzoquinone (18). *m*-Aminophenol (155 mg, 1.42 mmol) and toluhydroquinone (345 mg, 2.78 mmol) were taken up in water (20 mL). Silver(I) oxide (68 mg, 0.29 mmol) was added and the reaction mixture was stirred vigorously for 5 minutes. With a gas outlet attached, aqueous hydrogen peroxide (30% v/v, 3 mL) was added gradually over 20 minutes with continued vigorous stirring. Brine (40 mL) was added and the mixture was extracted with dichloromethane (4 × 100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel, eluting with 25% ethyl acetate in light petroleum, gave compound **18** (173 mg, 53%) as a dark purple solid; R_f = 0.18 (20% ethyl acetate in light petroleum); mp 116 °C; λ_{max} (MeOH)/nm 502 (ε 3120); ν_{max} (solid)/cm^{-1} 3252, 1671, 1644, 1585, 1463, 1296, 1212, 1160, 1008; δ_H (300 MHz; DMSO-d^6); 9.58 (1 H, br s), 8.76 (1 H, br s), 7.16 (1 H, t, *J* = 7.8 Hz), 6.76-6.74 (2 H, m), 6.64-6.55 (2 H, m), 5.93 (1 H, s), 1.95 (3 H, s); δ_C (75 MHz; DMSO-d^6) 185.8 (C), 183.7 (C), 158.0 (C), 148.3 (C), 144.1 (C), 139.2 (C), 130.0 (CH), 129.6 (CH), 113.7 (CH), 112.1 (CH), 109.7 (CH), 100.0 (CH), 15.8 (CH_3); HRMS (APCI) Found MH^+ 230.0810. $C_{13}H_{12}NO_3^+$ requires 230.0812.

3-Aminophenyl acetate (20). To a mixture of *m*-aminophenol (1.1 g, 10 mmol) and 4-dimethylaminopyridine (100 mg.) was added a solution of acetic anhydride (0.83 mL, 8.8 mmol) and triethylamine (1.24 mL, 8.90 mmol) in dichloromethane (75 mL). The reaction mixture was stirred overnight at room temperature, and then concentrated *in vacuo*. Flash chromatography on silica gel, eluting with 20% ethyl acetate in light petroleum, gave compound **20** (1.29 g, 97%) as a light yellow oil which solidified upon standing; R_f = 0.16 (20% ethyl acetate in light petroleum); ν_{max} (oil)/cm^{-1} 3370, 1735, 1605, 1489, 1369, 1203, 1141, 1014; δ_H (300 MHz; $CDCl_3$) 7.09 (1 H, t, *J* = 8.1 Hz), 6.48-6.43 (2 H, m), 6.35-6.34 (1 H, m), 3.91 (2 H, br s, NH_2), 2.24 (3 H, s); δ_C (75 MHz; $CDCl_3$) 169.6 (C), 151.5 (C), 147.9 (C), 129.8 (CH), 112.5 (CH), 110.8 (CH), 108.1 (CH), 20.9 (CH_3).

2-(2-Acetoxyanilino)-5-methyl-1,4-benzoquinone (21). A*cetylation route:* To a mixture of compound **18** (560 mg, 2.50 mmol) and 4-dimethylaminopyridine (30 mg) was added a solution of triethylamine (350 µL, 2.50 mmol) and acetic anhydride (240 µL, 2.50 mmol) in dichloromethane (50 mL). The reaction mixture was stirred at room temperature for 2 hours and was then concentrated *in vacuo*. Flash chromatography on silica gel, eluting with 10% ethyl acetate in light petroleum, gave the desired compound **21** (94 mg, 14%) as a purple solid; R_f = 0.35 (20% ethyl acetate in light petroleum); mp 169-171 °C; λ_{max} (MeOH)/nm 490 (ε 4110); ν_{max} (oil)/cm^{-1} 2932, 1824, 1756, 1645, 1493, 1368, 1208, 1167, 1118; δ_H (300 MHz; $CDCl_3$) 7.37 (1 H, dd, *J* = 8.1, 8.1 Hz), 7.30 (1 H, br s, NH), 7.06 (1 H, dd, *J* = 8.1, 1.2 Hz), 6.99 (1 H, dd, *J* = 2.1, 2.1 Hz), 6.90 (1 H, dd, *J* = 8.1, 1.8 Hz), 6.57 (1 H, d, *J* = 1.5 Hz), 6.20 (1 H, s), 2.31 (3 H, s), 2.09 (3 H, d, *J* = 1.5 Hz); δ_C (75 MHz; $CDCl_3$) 186.7 (C), 183.5 (C), 169.1 (C), 151.4 (C), 149.4 (C), 142.5 (C), 138.7 (C), 130.3 (CH), 129.4 (CH), 119.1 (CH), 118.2 (CH), 115.1 (CH), 101.6 (CH), 20.7 (CH_3), 16.3 (CH_3); HRMS (ESI) Found MH^+ 272.0921. $C_{15}H_{14}NO_4^+$ requires 272.0917.

In water, on water route: compound **20** (176 mg, 1.16 mmol) and toluhydroquinone (290 mg, 2.34 mmol, 2 eq.) were taken up in distilled water (20 mL). Silver(I) oxide (535 mg, 2.31 mmol, 2 eq.) was added and the reaction mixture was stirred vigorously for 5 minutes. With a gas outlet attached, aqueous hydrogen peroxide (30% v/v, 3 mL) was added gradually over 20 minutes with continued vigorous stirring. Brine (10 mL) was added the mixture was extracted with dichloromethane (4 × 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel, eluting with 10% ethyl acetate in light petroleum, gave the desired compound **21** (43 mg, 14%) as a dark red oil.

7-Acetoxy-3-methylcarbazole-1,4-quinone (22). To a solution of compound **21** (42 mg, 0.15 mmol) in glacial acetic acid (5 mL) was added palladium acetate (37 mg, 0.17 mmol). The mixture was heated under reflux for 1 hour then filtered through a pad of Celite™. The filtrate was extracted with ethyl acetate (3 × 30 mL), washed with water (3 × 30 mL) and saturated aqueous sodium hydrogencarbonate solution (50 mL), dried over Na_2SO_4 and solvent was removed *in vacuo*. Flash chromatography on silica gel, eluting with 20% ethyl acetate in light petroleum, gave the desired compound **22** (29 mg, 71% as a 3:1 mixture of isomers); an orange solid; R_f = 0.42 (20% ethyl acetate in light petroleum); mp 185 °C (decomp.); λ_{max} (MeOH)/nm 380 (ε 2550); ν_{max} (film)/cm^{-1} 2917, 1755, 1735, 1649, 1608, 1527, 1421, 1368, 1180, 1127, 1099, 1015, 1006; δ_H (300 MHz; DMSO-d^6) *major:* 7.46-7.35 (2 H, m), 6.96 (1 H, dd, *J* = 7.3, 1.0 Hz), 6.63 (1 H, q, *J* = 1.6 Hz), 2.44 (3 H, s), 2.04 (3 H, s); *minor:* 8.00 (1 H, d, *J* = 8.7 Hz), 7.27 (1 H, d, *J* = 1.8 Hz), 7.07 (1 H, dd, *J* = 8.7, 2.0 Hz), 6.57 (1 H, q, *J* = 1.6 Hz), 2.29 (3 H, s), 2.04 (3 H, s); δ_C (75 MHz; DMSO-d^6) *major:* 181.3 (C), 179.9 (C), 169.5 (C), 148.7 (C), 144.8 (C), 139.2 (C), 136.8 (C), 131.1 (CH), 126.7 (CH), 118.1 (C), 116.4 (CH), 114.6 (C), 111.7 (CH), 21.4 (CH_3), 16.3 (CH_3); *minor:* 183.0 (C), 179.8 (C), 169.4 (C), 149.0 (C), 147.8 (C), 137.6 (C), 136.6 (C), 131.6 (CH), 122.3 (CH), 121.3 (C), 118.9 (CH), 115.4 (C), 106.6 (CH), 21.0 (CH_3), 15.5 (CH_3); HRMS (ESI) Found MNa^+ 292.0573. $C_{15}H_{11}NO_4Na^+$ requires 292.0580.

7-Hydroxy-3-methylcarbazole-1,4-quinone (17). *Demethylation route*: To a solution of koeniginequinone A (**7**) (63 mg, 0.26 mmol) in dichloromethane (30 mL) was added a solution of sodium dithionite (200 mg) in distilled water (20 mL). The mixture was shaken vigorously until the organic phase was pale yellow, then the organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo*. The resulting pale yellow solid was immediately dissolved in dichloromethane (20 mL) under an inert atmosphere. Tetra-*n*-butylammonium iodide (230 mg, 0.62 mmol, 2.4 eq) was added and the

reaction mixture was cooled to 0 °C. Boron tribromide (1.0 M solution in dichloromethane; 1.2 mL, 1.2 mmol) was added and the reaction mixture was stirred at 0 °C for 30 minutes, then heated to reflux overnight. Deionised water (5 mL) was slowly added at 0 °C and the reaction mixture was allowed to stir open to air for 10 minutes. The resulting mixture was diluted with saturated ammonium chloride solution (30 mL) and extracted with dichloromethane (2 × 30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel, eluting with 10% acetone in dichloromethane, gave the desired compound **17** (45 mg, 76%) as a brown solid; R_f = 0.18 (10% acetone in dichloromethane); mp >300 °C (lit.[21] mp >300 °C); λ_{max} (MeOH)/nm 396 (ε 3150), 507 sh (1230); ν_{max} (solid)/cm^{-1} 3215, 1632, 1603, 1539, 1437, 1382, 1262, 1227; δ_H (300 MHz; DMSO-d_6) 12.33 (1 H, s), 9.72 (1 H, s), 7.78 (1 H, d, *J* = 5.8 Hz), 6.82-6.80 (2 H, m), 6.43 (1 H, s), 1.98 (3 H, s); δ_C (75 MHz; DMSO-d_6) 183.3 (C), 179.4 (C), 156.9 (C), 147.0 (C), 139.3 (C), 134.7 (C), 131.5 (CH), 122.5 (CH), 117.0 (C), 116.1 (C), 115.4 (CH), 97.5 (CH), 15.5 (CH_3); HRMS (APCI) Found MH^+ 228.0654. $C_{13}H_{10}NO_3^+$ requires 228.0655.

Hydrolysis route: To a solution of compound **22** (25 mg, 0.093 mmol) in methanol (5 mL) was added a methanolic solution of potassium carbonate (10% w/w; 2 mL) and the reaction mixture was stirred at room temperature for 2 hours. Saturated aqueous ammonium chloride (10 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo* to give the desired compound **17** (17 mg, 80%) as a brown solid.

3-Methyl-7-((2-methylbut-3-en-2-yl)oxy)carbazole-1,4-quinone (15). To a solution of **17** (28 mg, 0.12 mmol) in THF (2 mL) was added carbonate **25** (50 mg, 0.27 mmol) and tetrakis(triphenylphosphine) palladium(0) (3 mg, 0.003 mmol). The reaction mixture stirred at room temperature for 24 hr and was then diluted with ethyl acetate (5 mL), washed with brine (5 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. Flash chromatography on silica gel, eluting with 20% ethyl acetate in light petroleum, gave the desired compound **15** (17 mg, 47% [73% brsm]) as a brown solid; R_f = 0.39 (20% ethyl acetate in light petroleum); mp 100-102 °C; λ_{max} (MeOH)/nm 414 (ε 1640); ν_{max} (solid)/cm^{-1} 3281, 2923, 1606, 1528, 1467, 1375, 1257, 1141; δ_H (300 MHz; $CDCl_3$) 9.43 (1 H, br s, NH), 8.04 (1 H, d, *J* = 8.6 Hz), 7.09-7.00 (2 H, m), 6.46 (1 H, q, *J* = 1.6 Hz), 6.18 (1 H, dd, *J* = 10.8 Hz, 17.6 Hz, C<u>H</u>CH_2), 5.24-5.16 (2 H, m, CHC<u>H_2</u>), 2.15 (3 H, d *J* = 1.6 Hz), 1.50 (6 H, s); δ_C (75 MHz; $CDCl_3$) 183.8 (C), 180.1 (C), 156.2 (C), 148.5 (C), 144.3 (CH), 138.0 (C), 135.1 (C), 131.8 (CH), 123.1 (CH), 120.9 (CH), 119.7 (C), 117.3 (C), 114.0 (CH_2), 104.0 (CH), 80.5 (C), 27.2 (2 CH_3), 16.3 (CH_3); HRMS (ESI) Found MNa^+ 318.1100. $C_{18}H_{17}NO_3Na^+$ requires 318.1101.

Murrayaquinone E (14).[33] Water (5 mL) was added to compound **15** (13 mg, 0.041 mmol) and the reaction mixture was stirred vigorously at 80 °C for 24 hours. Brine (10 mL) was added and the mixture extracted with diethyl ether (2 × 10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. Flash chromatography on silica gel, eluting with 20% ethyl acetate in light petroleum, gave murrayaquinone E **(14)** (12 mg, 92%) as a brown solid; R_f = 0.16 (20% ethyl acetate in light petroleum); mp 88-89 °C; λ_{max} (MeOH)/nm 381 (ε 1460); ν_{max} (solid)/cm^{-1} 3231 br, 2924, 2854, 1632, 1534, 1466, 1377, 1261, 1158; δ_H (300 MHz; acetone-d^6) 10.98 (1 H, br s), 8.53 (1 H, br s), 7.82 (1 H, d, *J* = 8.7 Hz), 6.99 (1 H, d, *J* = 8.7 Hz), 6.45 (1 H, s), 5.32 (1 H, t, *J* = 6.6 Hz), 3.69 (2 H, d, *J* = 6.6 Hz), 2.08 (3 H, m, CH_3 + solvent), 1.80 (3 H, s), 1.66 (3 H, s); δ_C (75 MHz; acetone-d^6) 184.4 (C), 180.1 (C), 154.7 (C), 148.2 (C), 139.5 (C), 136.1 (C), 132.6 (C), 132.5 (CH), 123.3 (CH), 121.1 (CH), 119.0 (C), 118.1 (C), 116.0 (CH), 112.1 (C), 25.8 (CH_3), 24.2 (CH_2), 18.1 (CH_3), 15.8 (CH_3); HRMS (APCI) Found MNa^+ 318.1100. $C_{18}H_{17}NO_3Na^+$ requires 318.1101.

Murrayaquinone B (11).[34] To a solution of murrayaquinone E (**14**) (5 mg, 17 µmol) in THF (3 mL) at -78 °C was added *n*-butyllithium (8 µL, 2.15 M in hexanes, 17 µmol, 1 eq.) then iodomethane (53 µL, 850 µmol, 50 eq.), and the reaction was allowed to return to room temperature overnight. Water (10 mL) was added and the mixture extracted with diethyl ether (3 × 10 mL), dried over Na_2SO_4 and solvent removed *in vacuo*. Flash chromatography on silica gel, eluting with 10% ethyl acetate in light petroleum, gave murrayaquinone B **(11)** (5 mg, 95%) as a brown solid: R_f = 0.49 (20% ethyl acetate in light petroleum); mp 206-208 °C, (lit.[34] mp 221-223 °C); λ_{max} ($CHCl_3$)/nm 403 (ε 1000), 499 sh (370); ν_{max} (film)/cm^{-1} 3290, 2921, 2852, 1643, 1618, 1538, 1514, 1471, 1290, 1261, 1177, 1142, 1085; δ_H (300 MHz; $CDCl_3$) 8.85 (1 H, br s, NH), 8.02 (1 H, d, *J* = 8.8 Hz), 7.04 (1 H, d, *J* = 8.8 Hz), 6.45 (1 H, q, *J* = 1.6 Hz), 5.26 (1 H, t, *J* = 6.8 Hz), 3.92 (3 H, s), 3.58 (2 H, d, *J* = 6.8 Hz), 2.15 (3 H, d, *J* = 1.5 Hz), 1.86 (3 H, s), 1.76 (3 H, s); δ_C (75 MHz; $CDCl_3$) 183.9 (C), 180.0 (C), 156.2 (C), 148.4 (C), 138.1 (C), 135.2 (C), 134.3 (C), 131.7 (CH), 121.7 (CH), 121.3 (CH), 119.2 (C), 117.4 (C), 112.7 (C), 110.9 (CH), 56.9 (CH_3), 25.8 (CH_3), 23.9 (CH_2), 18.2 (CH_3), 16.3 (CH_3); HRMS (ESI) Found MH^+ 310.1437. $C_{19}H_{20}NO_3^+$ requires 310.1438.

7-((3,7-Dimethylocta-1,6-dien-3-yl)oxy)-3-methyl-carbazole-1,4-quinone (16). To a solution of **17** (29 mg, 0.13 mmol) in THF (0.25 mL) was added carbonate **26** (50 mg, 0.20 mmol) and tetrakis(triphenylphosphine) palladium(0) (7.5 mg, 0.006 mmol). The mixture was stirred at room temperature for 4 hours. Direct flash chromatography on silica gel, eluting with 20% ethyl acetate in light petroleum, gave the desired compound **16** (30 mg, 65% [90% brsm]) as a brown solid; R_f = 0.24 (10% ethyl acetate in light petroleum); mp 144-148 °C; λ_{max} ($CHCl_3$)/nm 412 (ε 900); ν_{max} (film)/cm^{-1} 3197, 2921, 2852, 1634, 1603, 1534, 1435, 1381, 1259, 1238, 1141, 1100; δ_H (300 MHz; $CDCl_3$) 8.93 (1 H, br s, NH), 8.04 (1 H, d, *J* = 8.5 Hz), 7.04-7.01 (2 H, m), 6.45 (1 H, q, *J* = 1.5 Hz), 6.13 (1 H, dd, *J* = 17.6, 11.0 Hz), 5.23 (1 H, d, *J* = 11.0 Hz), 5.21 (1 H, d, *J* = 17.6 Hz), 5.12 (1 H, t, *J* = 7.1 Hz), 2.17-2.09 (2 H, m), 2.15 (3 H, d, *J* = 1.5 Hz), 1.88-1.72 (2 H, m), 1.69 (3 H, s), 1.59 (3 H, s), 1.46 (3 H, s); δ_C (75 MHz; $CDCl_3$) 183.9, 179.9, 156.4, 148.4, 143.6, 137.8, 135.0, 132.0, 131.7, 124.1, 123.2, 120.6, 119.5, 117.4, 114.8,

103.2, 82.6, 41.8, 25.8, 22.9, 22.6, 17.8, 16.3; HRMS (ESI) Found MNa^+ 386.1730. $C_{23}H_{25}NO_3Na^+$ requires 386.1727.

Murrrayaquinone D (13).[34] Water (5 mL) was added to compound **16** (10 mg, 0.034 mmol) and the reaction mixture was stirred vigorously at 80 °C overnight. Brine (10 mL) was added and the mixture extracted with diethyl ether (2 × 10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. Flash chromatography on silica gel, eluting with 10% ethyl acetate in light petroleum, gave murrayaquinone D (**13**) (8 mg, 80%, E:Z/1.4:1) as a dark solid; R_f = 0.13 (10% ethyl acetate in light petroleum); mp 154-156 °C (lit.[34] mp 164-168 °C); λ_{max} ($CHCl_3$)/nm 403 (ε 2200), 500 (sh 880); ν_{max} (film)/cm^{-1} 3289 (br), 2957, 2924, 2854, 1636, 1607, 1530, 1468, 1378, 1285, 1261, 1171, 1142; δ_H (300 MHz; $CDCl_3$) 9.02 (1 H, br s, NH), 7.94 (1 H, d, *J* = 8.6 Hz), 6.88 (1 H, d, *J* = 8.7 Hz), 6.45 (1 H, s), 5.41 (1 H, br s, OH), 5.33 (1 H, t, *J* = 6.8 Hz), 5.17 (1 H, t, *J* = 6.3 Hz), 5.05 (1 H, m), 3.58 (2 H, d, *J* = 6.6 Hz), 2.31-2.10 (4 H, m), 2.14 (3 H, s), 1.86 (3 H, s), 1.80 (3 H, s), 1.69 (3 H, s), 1.64 (3 H, s), 1.58 (3 H, s); δ_C (75 MHz; $CDCl_3$) 184.0, 179.9, 153.4, 153.2, 148.3, 140.1, 140.0, 138.1, 134.8, 132.9, 132.3, 131.7, 123.7, 123.7, 121.7, 121.3, 120.5, 119.0, 117.7, 115.9, 115.8, 109.6, 109.6, 39.8, 32.3, 26.5, 26.4, 25.9, 25.8, 24.3, 24.0, 23.5, 17.9, 16.6, 16.3; HRMS (ESI) Found MNa^+ 386.1726. $C_{23}H_{25}NO_3Na^+$ requires 386.1727.

Murrayaquinone C (12).[34] To a solution of murrayaquinone D (**13**) (3.5 mg, 9.6 µmol) in THF (2 mL) at -78 °C was added *n*-butyllithium (4.5 µL, 2.2 M in hexanes, 9.9 µmol, 1 eq.) then iodomethane (30 µL, 480 µmol, 50 eq.), and the reaction was allowed to return to room temperature overnight. Water (10 mL) was added and the mixture extracted with diethyl ether (3 × 10 mL), dried over Na_2SO_4 and solvent removed *in vacuo*. Flash chromatography on silica gel, eluting with 10% ethyl acetate in light petroleum, gave murrayaquinone C **(12)** (2.5 mg, 70%, E:Z/1.2:1) as a brown solid; R_f = 0.56 (20% ethyl acetate in light petroleum); mp 94-104 °C, (lit.[34] mp 158-159 °C); λ_{max} ($CHCl_3$)/nm 402 (ε 2310), 503 (790); ν_{max} (film)/cm^{-1} 2956, 2924, 2854, 1643, 1620, 1539, 1511, 1465, 1257, 1087; δ_H (500 MHz; $CDCl_3$) 9.11 (1 H, br s, NH), 9.08 (1 H, br s, NH), 8.01 (1 H, d, *J* = 8.5 Hz), 8.00 (1 H, d, *J* = 8.5 Hz), 7.03 (1 H, d, *J* = 9.0 Hz), 7.02 (1 H, d, *J* = 9 Hz), 6.42 (1 H, m), 5.29-5.25 (1 H, m), 5.18 (1 H, t, *J* = 7.0 Hz), 5.05 (1 H, t, *J* = 7.0 Hz), 3.91 (3 H, s), 3.90 (3 H, s), 3.60-3.58 (2 H, m), 2.19-2.03 (4 H, m), 2.13 (3 H, *d*, J = 1.5 Hz), 1.85 (3 H, s), 1.75 (3 H, s), 1.68 (3 H, s), 1.64 (3 H, s), 1.61 (3 H, s), 1.56 (3 H, s); δ_C (125 MHz; $CDCl_3$) 183.9, 179.9, 156.2, 156.1, 148.3, 138.1, 137.7, 135.3, 131.8, 131.6, 131.6, 124.0, 122.3, 121.6, 121.3, 121.2, 119.2, 117.3, 112.8, 110.9, 110.8, 56.8, 56.8, 39.8, 32.3, 26.7, 26.5, 25.8, 25.7, 23.8, 23.6, 23.5, 17.8, 17.8, 16.5, 16.2; HRMS (ESI) Found MNa^+ 400.1887. $C_{24}H_{27}NO_3Na^+$ requires 400.1883.

Pyrayaquinone C (27).[23] To a solution of murrayaquinone D (**13**) (6.5 mg, 0.018 mmol) in toluene (1 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (4 mg, 0.018 mml). A few drops of 1,4-dioxane were added and the reaction mixture was heated to 80 °C for 3 hours. Brine (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. Flash chromatography on silica gel, eluting with 10% ethyl acetate in light petroleum, gave pyrayaquinone C (**27**) (6.2 mg, 96%) as a purple solid; R_f = 0.44 (20% ethyl acetate in light petroleum); mp 215-222 °C, (lit.[23] mp 223 °C); λ_{max} (MeOH)/nm 410 (ε 1980); ν_{max} (film)/cm^{-1} 3267, 2923, 1636, 1606, 1467, 1262; δ_H (300 MHz; $CDCl_3$) 9.30 (1 H, br s), 7.94 (1 H, d, *J* = 8.7 Hz), 6.86 (1 H, dd, *J* = 8.7, 0.4 Hz), 6.65 (1 H, d, *J* = 9.9 Hz), 6.46 (1 H, q, *J* = 1.7 Hz), 5.68 (1 H, d, *J* = 10.0 Hz), 5.09 (1 H, t, *J* = 7.1 Hz), 2.15 (3 H, d, *J* = 1.7 Hz), 2.13 (2 H, m), 1.80-1.70 (2 H, m), 1.66 (3 H, s), 1.57 (3 H, s), 1.44 (3 H, s); δ_C (75 MHz; $CDCl_3$) 183.9 (C), 180.0 (C), 152.9 (C), 148.4 (C), 134.8 (C), 134.3 (C), 132.1 (C), 131.8 (CH), 129.7 (CH), 124.0 (CH), 123.3 (CH), 119.0 (C), 117.9 (C), 116.4 (CH), 116.2 (CH), 105.5 (C), 79.3 (C), 41.1 (CH_2), 26.3 (CH_3), 25.8 (CH_3), 22.9 (CH_2), 17.8 (CH_3), 16.3 (CH_3); HRMS (APCI) Found 362.1750. $C_{23}H_{24}NO_3^+$ requires 362.1751.

Pyrayaquinone B (28).[22] To a solution of murrayaquinone E (**14**) (9.3 mg, 0.032 mmol) in toluene (1.75 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (7 mg, 0.031 mmol). A few drops of 1,4-dioxane were added and the reaction mixture was heated to 80 °C for 1 hour. Brine (10 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. Flash chromatography on silica gel, eluting with 10% ethyl acetate in light petroleum, gave pyrayaquinone B (**28**) (6.5 mg, 70%) as a purple solid; R_f = 0.41 (20% ethyl acetate in light petroleum); mp 247-254 °C, (lit.[22] mp 244 °C); λ_{max} ($CHCl_3$)/nm 412 (ε 3110), 512 (sh, 970); ν_{max} (film)/cm^{-1} 3274, 2920, 1632, 1610, 1580, 1539, 1464, 1267, 1136; δ_H (400 MHz; acetone-d^6) 7.89 (1 H, d, *J* = 8.7 Hz), 7.06 (1 H, dd, *J* = 9.9, 0.5 Hz), 6.84 (1 H, dd, *J* = 8.7, 0.6 Hz), 6.49 (1 H, q, *J* = 1.6 Hz), 5.81 (1 H, d, *J* = 9.9 Hz), 2.09 (3 H, d, *J* = 1.6 Hz), 1.46 (6 H, s); δ_C (100 MHz; acetone-d^6) 184.3 (C), 180.2 (C), 153.0 (C), 148.4 (C), 136.4 (C), 135.5 (C), 132.5 (CH), 131.0 (CH), 123.2 (CH), 119.8 (C), 117.9 (C), 117.6 (CH), 116.2 (CH), 107.2 (C), 77.2 (C), 27.9 (2 CH_3), 15.8 (CH_3); HRMS (APCI) Found 294.1124 $C_{18}H_{16}NO_3^+$ requires 294.1125.

N-Allyl-murrayaquinone A (34). To a solution of murrayaquinone A (39 mg, 0.18 mmol) in dichloromethane (10 mL) was added a solution of sodium dithionite (20 mg) in distilled water (10 mL). The mixture was shaken vigorously until the organic phase was colourless, which was then collected, dried over Na_2SO_4 and the solvent removed *in vacuo*. The resulting white solid was immediately dissolved in DMF (1 mL) under an inert atmosphere and added to a suspension of sodium hydride (23 mg, 60% in mineral oil, 3.1 eq.) in DMF (1 mL) at 0 °C. Allyl bromide (50 µL, 3.1 eq.) was added and the reaction mixture was stirred at room temperature overnight. Saturated NH_4Cl solution (10 mL) was added and the mixture was extracted with ethyl acetate (2 × 20 mL), washed with water (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4 and solvent removed *in vacuo*. Purified by flash chromatography on silica, eluting with 10% ethyl acetate in light petroleum, to give 9-allyl-1,4-bis(allyloxy)-3-methylcarbazole (14 mg, 23%) as a light yellow oil; R_f = 0.80

(10% ethyl acetate in light petroleum); ν_{max} (film)/cm^{-1} 2924, 2855, 1736, 1601, 1508, 1459, 1300, 1241, 1163, 1118; δ_H (300 MHz; $CDCl_3$) 8.24 (1 H, d, *J* = 7.8 Hz), 7.45-7.18 (3 H, m, ArH), 6.73 (1 H, s), 6.31-5.99 (3 H, m), 5.57-4.94 (8 H, m), 4.65 (2 H, d, *J* = 5.4 Hz), 4.55 (2 H, d, *J* = 5.4 Hz), 2.41 (3 H, s); 146.4 (C), 142.1 (C), 140.8 (C), 134.6 (CH), 134.3 (CH), 133.7 (CH), 129.7 (C), 125.4 (CH), 122.8 (CH), 121.8 (C), 120.4 (C), 119.4 (CH), 118.3 (C), 117.6 (CH_2), 117.3 (CH_2), 115.9 (CH_2), 111.9 (CH), 109.0 (CH), 73.5 (CH_2), 70.4 (CH_2), 47.5 (CH_2), 15.8 (CH_3); HRMS (ESI) Found MH^+ 334.1802. $C_{22}H_{24}NO_2^+$ requires 334.1807.

To a solution of this residue (14 mg, 0.042 mmol) in acetonitrile (1 mL) at 0 °C was added dropwise a solution of cerium ammonium nitrate (46 mg, 2 eq.) in water (1 mL) and the mixture was stirred for 10 minutes at 0 °C. Diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica, eluting with 15% ethyl acetate in light petroleum, gave the desired compound **34** (10 mg, 95%) as a bright orange oil which solidified upon standing, R_f = 0.90 (30% ethyl acetate in light petroleum); mp 106-107 °C, ν_{max} (film)/cm^{-1} 2923, 2853, 1645, 1614, 1520, 1469, 1253, 1181; λ_{max} ($CHCl_3$)/nm 405 (ε 3700), 490 sh (1170); δ_H (300 MHz; $CDCl_3$) 8.30 (1 H, d, *J* = 7.8 Hz), 7.42-7.33 (3 H, m, ArH), 6.44 (1 H, d, *J* = 0.8 Hz), 6.06-5.93 (1 H, m), 5.25 (2 H, d, *J* = 5.1 Hz), 5.18 (1 H, d, *J* = 10.2 Hz), 5.04 (1 H, d, *J* = 17.1 Hz), 2.15 (3 H, d, *J* = 0.8 Hz); δ_C (75 MHz; $CDCl_3$) 183.8 (C), 181.3 (C), 147.7 (C), 138.9 (C), 133.6 (C), 132.9 (CH), 132.3 (CH), 126.9 (CH), 124.6 (CH), 124.0 (C), 123.3 (CH), 117.6 (CH_2), 117.3 (C), 111.4 (CH), 47.1 (CH_2), 15.9 (CH_3); HRMS (ESI) Found MH^+ 252.1019. $C_{16}H_{14}NO_2^+$ requires 252.1019.

9-Allyl-1,4-bis(allyloxy)-7-methoxy-3-methyl-9H-carbazole (36). To a solution of koeniginequinone-A (150 mg, 0.62 mmol) in dichloromethane (50 mL) was added a solution of sodium dithionite (200 mg) in distilled water (50 mL). The mixture was shaken vigorously until the organic phase was pale yellow, which was then collected, dried over Na_2SO_4 and the solvent removed *in vacuo*. The resulting pale yellow solid was immediately dissolved in DMF (3 mL) under an inert atmosphere and added to a suspension of sodium hydride (125 mg, 5 eq., 60% in mineral oil) in DMF (3 mL) at 0 °C. Allyl bromide (0.27 mL, 5 eq.) was added and the reaction mixture stirred at room temperature for 5 hours. Saturated NH_4Cl solution (10 mL) added and the mixture was extracted with ethyl acetate, washed with water (3 × 10 mL) and brine (10 mL), dried over Na_2SO_4 and solvent removed *in vacuo*. Flash chromatography on silica, eluting with 10% ethyl acetate in light petroleum, gave the desired compound **36** (53 mg, 24%) as a yellow oil; R_f = 0.55 (10% ethyl acetate in light petroleum); ν_{max} (film)/cm^{-1} 2922, 2855, 1607, 1493, 1454, 1408, 1377, 1341, 1208, 1171; δ_H (300 MHz; $CDCl_3$) 8.11 (1 H, d, *J* = 8.6 Hz), 6.86 (1 H, dd, *J* = 8.6, 2.3 Hz), 6.82 (1 H, d, *J* = 2.3 Hz), 6.68 (1 H, s), 6.33-5.99 (3 H, m), 5.59-4.97 (8 H, m), 4.66 (2 H, ddd, *J* = 5.3, 1.3, 1.3 Hz), 4.56 (2 H, ddd, *J* = 5.4, 1.4, 1.4 Hz), 3.92 (3 H, s), 2.42 (3 H, s); δ_C (75 MHz; $CDCl_3$) 158.9 (C), 145.7 (C), 142.2 (C), 141.9 (C), 134.6 (CH), 134.1 (CH), 133.7 (CH), 129.5 (C), 123.4 (CH), 120.6 (C), 118.3 (C), 117.5 (CH_2), 117.2 (CH_2), 115.9 (CH_2), 115.7 (C), 110.9 (CH), 107.8 (CH), 93.4 (CH), 73.3 (CH_2), 70.3 (CH_2), 55.7 (CH_3), 47.5 (CH_2), 15.7 (CH_3); HRMS (APCI) Found MH^+ 364.1907. $C_{23}H_{26}NO_3$ requires 364.1907.

9,9'-Diallyl-2,2'-dimethoxy-6,6'-dimethyl-[3,3'-bicarbazole]-5,5',8,8'-tetraone (37) and 9,9'-diallyl-5,5',8,8'-tetrakis(allyloxy)-2,2'-dimethoxy-6,6'-dimethyl-9H, 9'H-3,3'-bicarbazole (38). To a solution of compound **36** (50 mg, 0.14 mmol) in acetonitrile (30 mL) at 0 °C was added dropwise a solution of cerium ammonium nitrate (150 mg, 2 eq.) in water (30 mL) and the mixture was stirred for 10 minutes at 0 °C then at room temperature for 2 hours. Diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica, eluting with 10% ethyl acetate in light petroleum, gave compound **37** (5 mg, 13%) as an orange solid; R_f = 0.30 (30% ethyl acetate in light petroleum); mp 141 °C (dec.); ν_{max} (film)/cm^{-1} 2925, 1643, 1612, 1520, 1491, 1460, 1419, 1247, 1233, 1204, 1167, 1040; λ_{max} ($CHCl_3$)/nm 443 (ε 5700); δ_H (300 MHz; $CDCl_3$) 8.14 (2 H, s), 6.80 (2 H, s), 6.40 (2 H, s), 6.11-5.98 (2 H, m), 5.26-5.09 (8 H, m), 3.86 (6 H, s), 2.11 (6 H, s); δ_C (75 MHz; $CDCl_3$) 184.0 (2 C), 180.6 (2 C), 158.2 (2 C), 146.9 (2 C), 139.9 (2 C), 133.0 (2 CH), 132.7 (2 C), 132.4 (2 CH), 127.8 (2 C), 125.5 (2 CH), 117.9 (2 C), 117.8 (2 C), 117.5 (2 CH_2), 91.9 (2 CH), 56.1 (2 CH_3), 47.1 (2 CH_2), 15.8 (2 CH_3); HRMS (ESI) Found MH^+ 561.2022. $C_{34}H_{29}N_2O_6^+$ requires 561.2020.

and compound **38** (12 mg, 24%) as a light brown oil; R_f = 0.12 (10% ethyl acetate in light petroleum; ν_{max} (oil)/cm^{-1} 2923, 2854, 1626, 1509, 1454, 1310, 1211, 1164, 1141; δ_H (300 MHz; $CDCl_3$) 8.17 (2 H, s), 6.89 (2 H, s), 6.66 (2 H, s), 6.22-6.05 (6 H, m), 5.52-5.30 (6 H, m), 5.27-5.25 (4 H, m), 5.19-5.10 (6 H, m), 4.67 (4 H, d, *J* = 5.3 Hz), 4.55 (4 H, d, *J* = 5.6 Hz), 3.87 (6 H, s), 2.39 (6 H, s); δ_C (75 MHz; $CDCl_3$) 157.0 (2 C), 145.9 (2 C), 141.8 (2 C), 141.4 (2 C), 134.6 (2 CH), 134.5 (2 CH), 133.9 (2 CH), 129.5 (2 C), 125.9 (2 CH), 121.7 (2 C), 120.4 (2 C), 118.7 (2 C), 117.5 (4 CH_2), 116.0 (2 CH_2), 115.1 (2 C), 110.7 (2 CH), 91.6 (2 CH), 73.4 (2 CH_2), 70.4 (2 CH_2), 56.1 (2 CH_3), 47.7 (2 CH_2), 15.9 (2 CH_3); HRMS (APCI) Found 725.3585. $C_{46}H_{49}N_2O_6^+$ requires 725.3585.

7-Methoxy-3-methylcarbazole-1,4-diyl diacetate (41). To a solution of koeniginequinone A (**7**) (47 mg, 0.19 mmol) in dichloromethane (20 mL) was added a solution of sodium dithionite (200 mg) in distilled water (20 mL). The mixture was shaken vigorously until the organic phase was pale yellow, then the organic phase was collected, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The resulting pale yellow solid was immediately dissolved in dichloromethane (5 mL) under an inert atmosphere. 4-Dimethylaminopyridine (5 mg), triethylamine (60 µL, 0.43 mmol) and acetic anhydride (40 µL, 0.43 mmol) were added and the reaction mixture was stirred at room temperature overnight, and then concentrated *in vacuo*. Flash chromatography on silica gel, eluting with dichloromethane, gave the desired compound **41** (39 mg, 64%) as a viscous, light yellow oil; R_f = 0.22 (dichloromethane); ν_{max} (film)/cm^{-1} 3362, 2927, 1760, 1620, 1505, 1369, 1281, 1191, 1164, 1111, 1026; δ_H (300 MHz; $CDCl_3$) 8.08 (1 H, s, NH), 7.73

(1 H, d, *J* = 8.4 Hz), 6.95 (1 H, s), 6.83-6.78 (2 H, m), 3.84 (3 H, s), 2.53 (3 H, s), 2.34 (3 H, s), 2.28 (3 H, s); δ_C (75 MHz; $CDCl_3$) 169.1 (2 C), 159.4 (C), 141.4 (C), 140.6 (C), 132.9 (C), 131.1 (C), 122.4 (CH), 121.1 (C), 119.0 (CH), 118.7 (C), 115.3 (C), 109.1 (CH), 95.1 (CH), 55.6 (CH_3), 21.2 (CH_3), 21.0 (CH_3), 15.8 (CH_3); HRMS (ESI) Found MNa^+ 350.0999. $C_{18}H_{17}NO_5Na^+$ requires 350.0999.

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