Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 6105

Palladium mediated intramolecular multiple C–X/C–H cross coupling and C–H activation: synthesis of carbazole alkaloids calothrixin B and murrayaquinone A†

Srinivasan A. Kaliyaperumal, Shyamapada Banerjee and Syam Kumar U. K.*

Received 5th March 2014,
Accepted 9th April 2014

DOI: 10.1039/c4ob00493k

www.rsc.org/obc

Straightforward palladium mediated syntheses of calothrixin B and murrayaquinone A are described. Regioselective palladium mediated intramolecular multiple C–X/C–H cross coupling reaction on *N*-(4-((2-bromophenyl)amino)-2,5-dimethoxybenzyl)-*N*-(2-iodophenyl)acetamide followed by CAN oxidation afforded calothrixin B in excellent yield in two steps. A linear synthesis has also been developed for calothrixin B. Utilizing C–H functionalization as well as palladium mediated intramolecular C–X/C–H cross coupling reaction, murrayaquinone A synthesis was achieved. Overall, these synthetic methodologies provide an expedient entry to these biologically active alkaloids in a short reaction sequence.

Introduction

The pentacyclic carbazole alkaloids calothrixin A (**1**) and B (**2**) were isolated by Rickards *et al.* from *Calothrix cyanobacteria* in 1999.[1] Calothrixins possess an unprecedented indolo[3,2-*j*]-phenanthridine framework with a striking assemblage of quinoline, quinone and indole pharmacophores. Calothrixin A (**1**) and B (**2**) exhibited antimalarial activity as well as inhibitory effects on a chloroquine resistant strain of the malarial parasite *Plasmodium falciparum.*[2] Both **1** and **2** inhibit the growth of human HeLa cancer cell lines and act as inhibitors of bacterial-RNA polymerase.[3] Kelly *et al.*[4] reported the first total synthesis of calothrixins in 2000 utilizing an *ortho*-lithiation strategy. Several further elegant total syntheses of **1** and **2** were illustrated in the literature utilizing a hetero Diels–Alder protocol,[5] Friedel–Crafts reaction,[6] palladium mediated tandem cyclization–cross coupling reaction[7] C–H activation,[8] $FeCl_3$ mediated domino reaction[9] and radical assisted cyclization[10] as well as a biomimetic approach.[11] Murrayaquinone A (**3**) is an indole alkaloid isolated by Furukawa *et al.* from *Murraya euchrestifolia*.[12] The plant genus *Murraya* has been used as a folk medicine for analgesia and local anesthesia and also for the treatment of eczema, rheumatism and dropsy (Fig. 1).

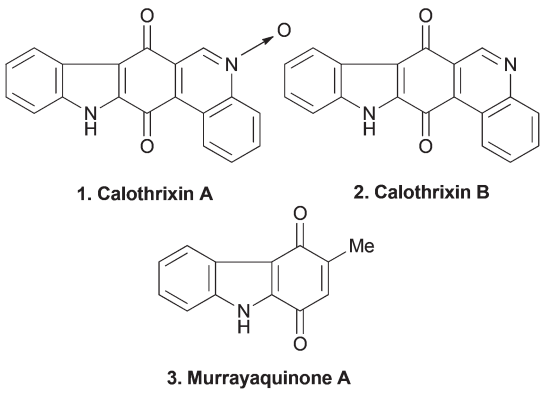


Fig. 1 Carbazole alkaloids.

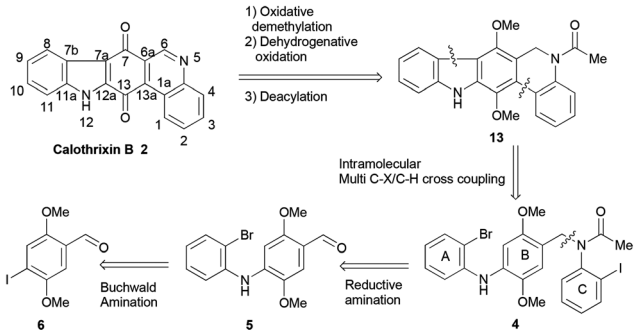
Results and discussion

Multiple Heck reaction of polyhaloarenes provides the opportunity for building several C–C bonds in a single synthetic operation,[13] however multiple intramolecular C–X/C–H cross coupling reactions are rarely explored.[14] Herein we report the total synthesis of calothrixin B (**2**) *via* multiple as well as stepwise palladium mediated intramolecular multiple C–X/C–H cross coupling reactions, and murrayaquinone A (**3**) synthesis by C–H activation and also by C–X/C–H cross coupling reaction from its basic starting materials.

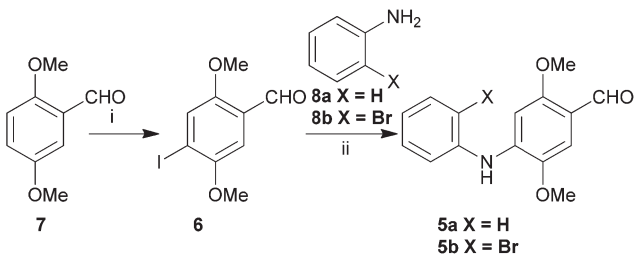
The disconnection strategy for the synthesis of calothrixin B (**2**) is depicted in Scheme 1. Calothrixin B (**2**) could be obtained by the oxidative demethylation, dehydrogenative oxidation and deacylation of **13**. The most salient features of our

Technology Development Centre, Custom Pharmaceutical Services, Dr Reddy's Laboratories Ltd, Miyapur, Hyderabad, 500 049, India. E-mail: syam_kmr@yahoo.com; Fax: +91 4044658699; Tel: +91 4044658618

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ob00493k



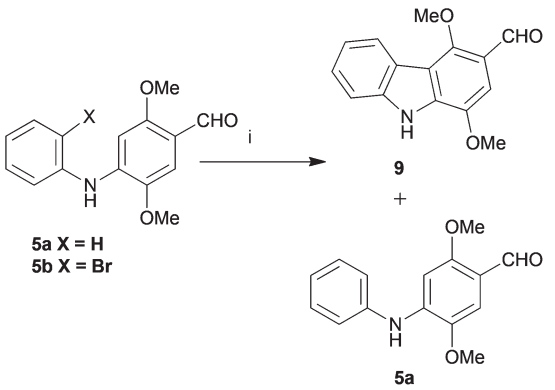
Scheme 1 Retrosynthetic analogy for calothrixin B.



Scheme 2 Buchwald–Hartwig amination. Reagents and conditions: (i) I_2, $AgNO_3$, MeOH, r.t., 12 h, 95%; (ii) Pd(dppf)Cl_2·CH_2Cl_2, (±)-BINAP, Cs_2CO_3, **8a** or **8b**, MeCN, 70 °C, 12 h (X = Br, 85%; X = H, 90%).

strategy are the creation of C7a–C7b and C13a–C1a bonds under palladium mediated intramolecular multiple C–X/C–H cross coupling reaction in a single synthetic operation from **4**. The substitution pattern on the A and C rings of **4** would allow the regioselective C–X/C–H cross couplings. The dihaloarene **4** could be accessed *via* the reductive amination of biarylaminoaldehyde **5** with aniline **10**. The iodoaldehyde **6** could be used as a synthetic precursor for palladium mediated Buchwald aryl amination reaction with **8** to access the biarylaminoaldehyde **5**.

The synthesis of the key intermediates 2,5-dimethoxy-4-(phenylamino)benzaldehyde **5a** and 2,5-dimethoxy-4-(2-bromophenylamino)benzaldehyde **5b** required for the preparation of calothrixin B (**2**) is outlined in Scheme 2. The synthesis of **5a** and **5b** were initiated with commercially accessible aldehyde **7**. The iodination of aldehyde **7** with a stoichiometric amount of iodine in the presence of silver nitrate afforded the iodo aldehyde **6** in 95% yield.[15] The Buchwald–Hartwig coupling reaction of amine **8b** with iodoaldehyde **6** was carried out with Pd(dppf)Cl_2·CH_2Cl_2, *rac*-BINAP and Cs_2CO_3 combination in acetonitrile at 60–70 °C for 10–12 hours, and produced **5b** in excellent yield. Though the Buchwald aryl amination of **6** with aryl halo amines is not well exemplified in the literature,[16] our attempted aryl amination reaction went very well, notably with less background reaction. Other phosphine ligands such as PPFA, PPFE, DPPP, DPPE, PPh_3 and P(*o*-tolyl)$_3$ were employed in the Buchwald amination, and gave either low conversion or poor product/reduced substrate ratios. To check the possibility of carbazole synthesis *via* C–H functionalization, **5a** was synthesized by the Buchwald–aryl amination protocol. Owing to the moderate conditions employed in the synthesis of **5b** *via* Buchwald amination reaction, no C–C bond formation and dehalogenation were observed.



Scheme 3 Synthesis of carbazole derivatives. Reagents and conditions: (i) X = H, Pd(OAc)$_2$ (2 equiv.), AcOH, 130 °C, 6 h, 91%; X = Br, Pd(OAc)$_2$, K_2CO_3, 10 mol% JohnPhos, 20 mol% PCy_3, MeCN, 100 °C, 12 h, 90%.

Initially the synthesis of carbazole **9** was attempted under intramolecular C–X/C–H cross coupling reaction conditions from **5b** (Scheme 3). To identify the appropriate conditions for palladium mediated intramolecular C–X/C–H cross coupling reaction, Pd(OAc)$_2$ was chosen as the catalyst and the reaction was attempted with various solvent–base combinations in the presence of phosphine ligands. The results of these studies are summarized in Table 1.

1,4-Dimethoxy-9*H*-carbazole-3-carbaldehyde (**9**) was obtained in good yield when the reaction was carried out with 5 mol% of Pd(OAc)$_2$, 20 mol% PCy_3 and 10 mol% JohnPhos in the presence of K_2CO_3 base in acetonitrile. The reaction was complete after 12 hours at 100 °C (entry 6) and afforded 9*H*-carbazole-3-carbaldehyde **9** in 90% yield along with a small percentage (7%) of **5a**.

We also extensively studied the C–H activation methodology for the construction of **9** (Table 2) from **5a** (Scheme 3). More importantly, the synthesis of carbazole by C–H activation was carried out in the absence of an oxidizing agent.

Unreacted starting material **5a** was significantly decreased when the C–H activation reactions were performed with stoichiometric amounts or excess of palladium acetate. Using 2 equiv. of Pd(OAc)$_2$, the complete consumption of **5a**, along with substantially higher yields of the desired product **9** (more than 90%), was achieved within 6 hours when the C–H activation reaction was conducted in acetic acid as solvent.

The direct reductive amination of **9** with 2-iodoaniline (**10**) was then carried out with sodium triacetoxyborohydride in the presence of TFA in isopropyl acetate solvent[17] and afforded **11** in 95% yield (Scheme 4).

The palladium mediated intramolecular C–X/C–H cross coupling reaction on **11** under various conditions failed to yield to the calothrixin framework probably due to electronic effects. To reduce the electron density and to afford effective coordination with Pd(II), *N*-acylation of **11** was carried out with

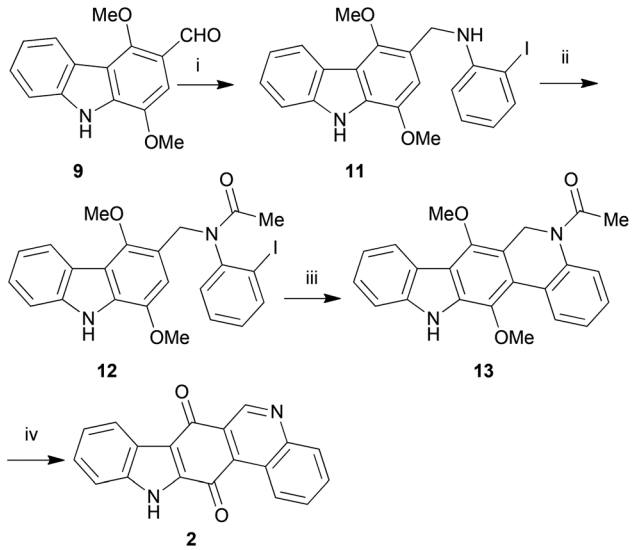
Table 1 Synthesis of carbazole **9** from **5b** by C–X/C–H cross coupling reaction

Entry	Catalyst	Solvent	Ligand	X	Time (h)	Yield (%) **5a**	Yield (%) **9**
1	5 mol% $Pd(OAc)_2$	Toluene	20 mol% PPh_3	Br	12	0	0
2	5 mol% $Pd(OAc)_2$	DMF	20 mol% PPh_3	Br	14	5	30
3	10 mol% $PdCl_2$	DMF	20 mol% PPh_3	Br	14	0	30
4	5 mol% $Pd(OAc)_2$	MeCN	20 mol% PPh_3	Br	16	0	20
5	5 mol% $Pd(OAc)_2$	MeCN	20 mol% PCy_3	Br	12	30	60
6	5 mol% $Pd(OAc)_2$	MeCN	20 mol% PCy_3 & 10 mol% JohnPhos	Br	12	7	90

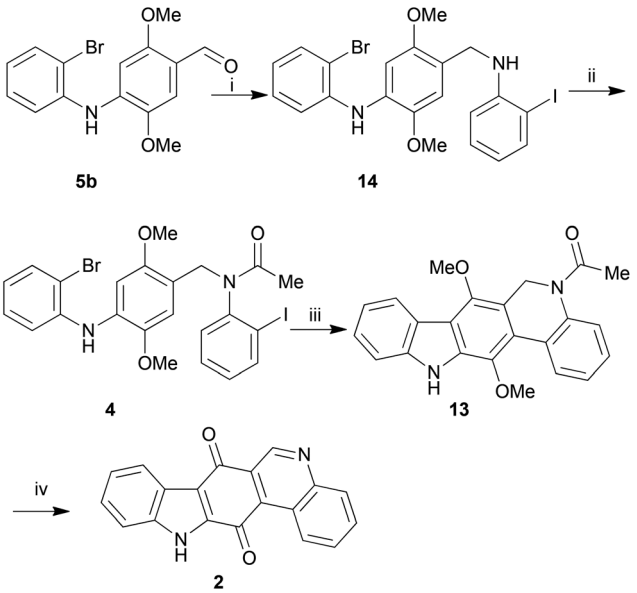
Table 2 Synthesis of carbazole **9** from **5a** by C–H activation reaction

Entry	Catalyst	Solvent	Ligand	Time (h)	X	Yield (%) **9**
1	5 mol% $Pd(OAc)_2$	Toluene	20 mol% PPh_3	24	H	0
2	5 mol% $Pd(OAc)_2$	DMF	20 mol% PPh_3	24	H	0
3	10 mol% $PdCl_2$	DMF	20 mol% PPh_3	24	H	0
4	5 mol% $Pd(OAc)_2$	MeCN	20 mol% PPh_3	24	H	0
5	5 mol% $Pd(OAc)_2$	AcOH	—	24	H	0[a]
6	0.5 equiv. $Pd(OAc)_2$	AcOH	—	24	H	30[a]
7	1 equiv. $Pd(OAc)_2$	AcOH	—	10	H	75[a]
8	2 equiv. $Pd(OAc)_2$	AcOH	—	6	H	91[a]

[a] Reaction was conducted in the absence of ligand and oxidizing agent.



Scheme 4 Iterative synthesis of calothrixin B (**2**). Reagents and conditions: (i) 2-iodoaniline (**10**), TFA, $NaBH(OAc)_3$, i-PrOAc, r.t., 10 min, 95%; (ii) NEt_3, AcCl, CH_2Cl_2, 5 °C to r.t., 2 h, 94%; (iii) $Pd(OAc)_2$, K_2CO_3, 20 mol% PCy_3, DMF, 110 °C, 10 h, 90%; (iv) CAN, MeCN–water, r.t., 2 h, 85%.



Scheme 5 Synthesis of calothrixin B (**2**) by intramolecular multiple C–X/C–H cross coupling reaction. Reagents and conditions: (i) 2-iodoaniline (**10**), TFA, $NaBH(OAc)_3$, i-PrOAc, r.t., 10 min, 95%; (ii) NEt_3, AcCl, CH_2Cl_2, 5 °C to r.t., 2 h, 94%; (iii) $Pd(OAc)_2$, K_2CO_3, 10 mol% JohnPhos, 30 mol% PCy_3, DMF, 110 °C, 10 h, 88%; (iv) CAN, MeCN–water, r.t., 2 h, 85%.

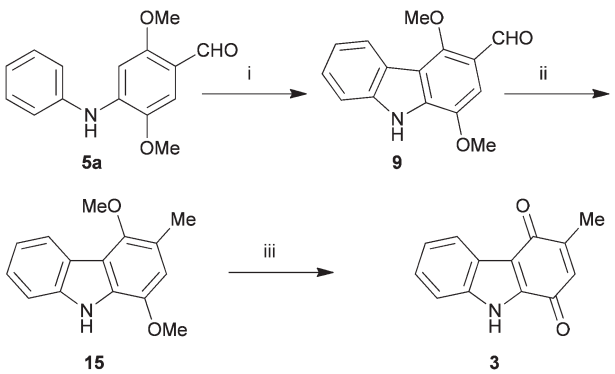
acetyl chloride in the presence of triethylamine in dichloromethane to afford **12**. Subsequently **12** was subjected to the intramolecular reaction using 5 mol% of $Pd(OAc)_2$, 20 mol% PCy_3 and powdered K_2CO_3 in DMF. The C–X/C–H cross coupling reaction proceeded as expected and **13** was isolated in 90% yield after purification.[18] CAN was found to be a very effective reagent for the oxidation of phenanthridine **13** to afford the corresponding quinone. However, during the oxidative demethylation of **13**, concomitant aromatization as well deacylation was observed and the natural alkaloid, calothrixin B (**2**), was obtained in 85% yield.

After the successful completion of the calothrixin B (**2**) synthesis *via* the iterative process, we focussed our attention towards the synthesis of **2** under double intramolecular C–X/C–H cross coupling reaction conditions (Scheme 5). Although

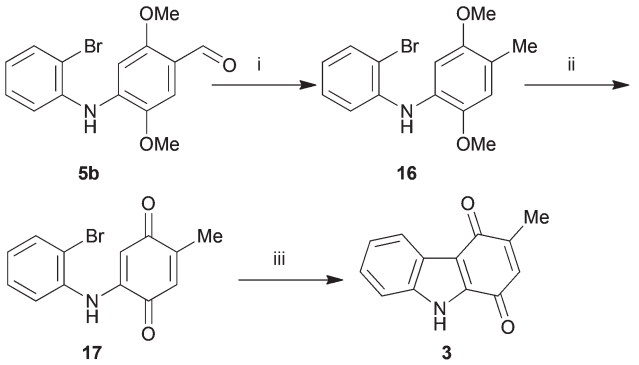
the use of the C–H activation methodology was initially planned for the construction of the C7a–C7b bond, owing to the high Pd(II) loading required for the reactions, an intramolecular multiple C–X/C–H cross coupling reaction was utilized for the synthesis of **2**, instead of the C–H activation methodology.

The reductive amination of 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (**5b**) with 2-iodoaniline (**10**) was then carried out with sodium triacetoxyborohydride in the presence of TFA in isopropyl acetate solvent and afforded **14** in 95% yield. The intermediate **14** has all the structural requisites for carrying out the multifold C–X/C–H cross coupling reaction to construct the framework of the alkaloid **2**. The acylation of **14** with acetyl chloride in the presence of triethylamine exclusively afforded **4** and no trace of the diacetyl product was observed in this reaction. The double intramolecular C–X/C–H cross coupling reaction was then attempted on **4** under several conditions and the best yield was obtained when the reaction was carried out with 5 mol% of $Pd(OAc)_2$ in the presence of 30 mol% of PCy_3 and 10 mol% of JohnPhos. The reaction went smoothly when performed with 4 equiv. of powdered K_2CO_3 in DMF at 110 °C. The progress of the reaction was monitored by LCMS, which clearly confirmed the early formation of the C13a–C1a bond leading to the phenanthridine framework, followed by C7a–C7b bond construction. This is probably due to the lower activation energy required for the insertion of the transition metal at the C13 position, because of the presence of an adjacent *N*-acetyl group. The oxidative demethylation, deacylation and further aromatization of **13** were carried out with CAN in a single pot reaction and produced the natural alkaloid **2** in good yield.

As part of these studies, we also synthesized murrayaquinone A (**3**) (Scheme 6). The carbazole-3-carbaldehyde **9** obtained by C–H activation of **5a** was subjected to reduction with TMSCl/TES to yield 3-methyl-9*H*-carbazole **15**. Owing to the decomposition of **15** under CAN oxidation conditions,[19] the demethylative oxidation of **15** was attempted with boron tribromide under aerial oxidation conditions as reported by Moody *et al.*[20] and the alkaloid **3** was isolated in 74% yield.



Scheme 6 Synthesis of murrayaquinone A (**3**) by C–H activation. Reagents and conditions: (i) $Pd(OAc)_2$, AcOH, 130 °C, 6 h, 91%; (ii) TMSCl, TES, MeCN, r.t., 4 h, 83%; (iii) BBr_3, CH_2Cl_2, –78 °C, 22 h, 74%.



Scheme 7 Synthesis of murrayaquinone A (**3**) *via* intramolecular C–X/C–H cross coupling reaction. Reagents and conditions: (i) TMSCl, TES, MeCN, r.t., 6 h, 80%; (ii) CAN, MeCN–water, r.t., 2 h, 88%; (iii) $Pd(OAc)_2$, K_2CO_3, 10 mol% JohnPhos, 20 mol% PCy_3, MeCN, 110 °C, 9 h, 88%.

In an alternative attempt to synthesize murrayaquinone **3** (Scheme 7), 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (**5b**) was reduced with TES/TMSCl conditions to afford **16**.

CAN oxidation of **16** followed by intramolecular C–X/C–H reaction using $Pd(OAc)_2$, PCy_3, JohnPhos and powdered K_2CO_3 afforded the natural alkaloid murrayaquinone A (**3**) in 88% yield.

Conclusion

In conclusion, two efficient protocols for the synthesis of calothrixin B (**2**) have been developed in overall excellent yields. These syntheses were achieved through the development of efficient mono and double C–X/C–H cross coupling reactions through the exploration of various palladium catalysts and ligands. Utilizing C–H activation as well as intramolecular C–X/C–H reaction protocols, murrayaquinone A (**3**) has also been synthesized. Studies are underway to expand the scope of these methodologies for the synthesis of more complex bisindole alkaloids.

Experimental section

General

All reactions were carried out in oven dried glassware under an atmosphere of N_2, with magnetic stirring and the reactions were monitored by TLC, using Merck aluminum-backed plates pre-coated with silica (0.25 mm, 60, F254). The TLC plates were visualized under UV light (254 nm) or developed using a solution of $KMnO_4$. Purifications were performed by column chromatography (CC) with silica gel (60–120 mesh) purchased from SRL and eluted with hexanes–EtOAc.

Mps were determined on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1650 Fourier Transform spectrometer. NMR

spectra were measured in $CDCl_3$, CD_3OD or DMSO-D_6 (all with TMS as an internal standard) on Varian Gemini 400 MHz FT magnetic resonance spectrometers. Chemical shifts are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded on an HP-5989A quadrupole mass spectrometer.

Procedure for 4-iodo-2,5-dimethoxybenzaldehyde (6)

A mixture of 2,5-dimethoxybenzaldehyde **7** (10.2 g, 61.4 mmol), silver nitrate (10.4 g, 61.4 mmol), and iodine (16.2 g, 64 mmol) in 250 mL of methanol was stirred under nitrogen overnight. The yellow precipitate was filtered and washed with methanol. The remaining iodine was reduced with saturated sodium bisulfite solution and the solvent was removed on a rotary evaporator and the residue recrystallized from 95% ethanol to yield the off-white title compound **6** (17.08 g, 95%).

Mp: 139–141 °C.[15] IR (ν_{max}/cm^{-1}) 3410, 2942, 1676, 1595, 1386, 1216, 1035 and 770. δ_H ($CDCl_3$, 400 MHz) 3.87 (s, 3H), 3.89 (s, 3H), 7.22 (s, 1H), 7.47 (s, 1H) and 10.40 (s, 1H). δ_C ($CDCl_3$, 100 MHz) 56.6, 56.7, 97.0, 107.5, 124.0, 124.3, 152.2, 155.7 and 188.4. LRMS (ESI) m/z = 293 $(M + H)^+$. HRMS (ESI) calcd for $C_9H_{10}IO_3$ $(M + H)^+$: 292.9675, found: 292.9674.

Procedure for the preparation of 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (5b)

A mixture of 4-iodo-2,5-dimethoxybenzaldehyde (**6**) (10 g, 34 mmol), 2-bromoaniline **8b** (5.9 g, 34 mmol), Pd(dppf)-Cl_2·CH_2Cl_2 (1.40 g, 1.7 mmol), (±)-2,2-bis(diphenylphosphino)-1,1′-binaphthyl [(±)-BINAP] (1.06 g, 1.7 mmol) and cesium carbonate (22 g, 68 mmol) in acetonitrile (150 mL) was stirred at 60–70 °C under N_2 for 12 hours (the reaction was monitored by TLC). The reaction mixture was filtered over a celite bed and washed with EtOAc. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 1 : 10) which gave the title compound **5b** as a pale yellow solid (9.8 g, 85%).

Mp: 124–126 °C. IR (ν_{max}/cm^{-1}) 3398, 3019, 2400, 1657, 1584, 1525, 1215. δ_H ($CDCl_3$, 400 MHz) 3.79 (s, 3H), 3.95 (s, 3H), 6.72 (s, 1H), 6.93–7.01 (m, 2H), 7.26–7.35 (m, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H) and 10.26 (s, 1H). δ_C ($CDCl_3$, 100 MHz) 56.1, 56.2, 95.6, 108.2, 116.3, 116.8, 121.2, 124.6, 128.2, 133.6, 138.2, 140.3, 141.9, 158.9 and 187.4. LRMS (ESI): m/z = 336, 338 $(M + H)^+$. HRMS (ESI) calcd for $C_{15}H_{15}BrNO_3$ $(M + H)^+$: 336.0235, found: 336.0231.

Procedure for the preparation of 2,5-dimethoxy-4-(phenylamino)benzaldehyde (5a)

The compound **5a** was prepared as shown in the general experimental procedure for **5b** and isolated as an off-white solid (7.9 g, 90%).

Mp: 122–124 °C. IR (ν_{max}/cm^{-1}) 3778, 3411, 3019, 2905, 2834, 1656, 1497, 1275, 1216. δ_H (DMSO-d_6, 400 MHz) 3.74 (s, 3H), 3.86 (s, 3H), 6.75 (s, 1H), 7.08 (td, J = 2.9, 5.4 Hz, 1H), 7.17 (s, 1H), 7.34–7.39 (m, 4H), 8.27 (s, 1H) and 10.09 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 55.8, 55.8, 94.8, 107.9, 114.3, 121.5 (2C), 123.1, 129.2 (2C), 140.2, 141.6, 141.8, 158.6 and 185.4. LRMS (ESI): m/z = 258 $(M + H)^+$. HRMS (ESI) calcd for $C_{15}H_{16}NO_3$ $(M + H)^+$: 258.1130, found: 258.1139.

Procedure for the preparation of 1,4-dimethoxy-9*H*-carbazole-3-carbaldehyde (9)

From 2,5-dimethoxy-4-(phenylamino)benzaldehyde (5a). A mixture of 2,5-dimethoxy-4-(phenylamino)benzaldehyde (**5a**) (0.5 g, 1.9 mmol) and palladium(II) acetate (0.873 g, 3.9 mmol) in glacial acetic acid (10 mL) was heated to 130 °C for 6 hours with gentle stirring under argon atmosphere. After the completion of the reaction, the mixture was cooled to room temperature and poured into aqueous sodium hydrogen carbonate solution (25 mL). Solid sodium hydrogen carbonate was added to the reaction mixture till it was neutral. The reaction mixture was extracted with EtOAc (3 × 30 mL) and the layers were separated. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 1 : 5) which gave the title compound **9** as a pale yellow solid (0.449 g, 91%).

From 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (5b). A mixture of 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (**5b**) (1 g, 2.9 mmol), powdered K_2CO_3 (0.823 g, 5.9 mmol), palladium(II) acetate (0.033 g, 0.1 mmol), tricyclohexylphosphine (0.167 g, 0.6 mmol) and 10 mol% of (2-biphenyl)di-*tert*-butylphosphine (JohnPhos) (0.089 g, 0.3 mmol) in acetonitrile (20 mL) was heated 100 °C for 12 hours with gentle stirring under argon atmosphere. After completion of the reaction, the mixture was filtered over a celite bed and washed with EtOAc. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 1 : 5) which gave the title compound **9** as a pale yellow solid (0.679 g, 90%).

Mp: 173–175 °C. IR (ν_{max}/cm^{-1}) 3349, 2851, 1657, 1622, 1586, 1340. δ_H (DMSO-d_6, 400 MHz) 4.02 (s, 3H), 4.09 (s, 3H), 7.24 (s, 1H), 7.31 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.3 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 10.36 (s, 1H) and 12.09 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 55.8, 63.7, 102.4, 112.1, 115.8, 119.8, 120.5, 120.9, 122.1, 126.0, 135.8, 139.7, 142.7, 155.4 and 187.8. LRMS (ESI): m/z = 256 $(M + H)^+$. HRMS (ESI) calcd for $C_{15}H_{14}NO_3$ $(M + H)^+$: 256.0974, found: 256.0973.

Procedure for *N*-((1,4-dimethoxy-9*H*-carbazol-3-yl)methyl)-2-iodoaniline (11)

A round bottomed flask was charged with 2-iodoaniline (**10**) (0.24 g, 1.1 mmol) and 1,4-dimethoxy-9*H*-carbazole-3-carbaldehyde (**9**) (0.28 g, 1.1 mmol) followed by i-PrOAc (6 mL) and trifluoroacetic acid (0.250 g, 2.2 mmol). Sodium triacetoxyborohydride (0.465 g, 2.2 mmol) was added as a solid over 2 min (an exothermicity was observed up to ~40 °C). After 10 min agitation, TLC showed the completion of the reaction. The

reaction mixture was diluted with EtOAc (20 mL). A solution of 2 wt% of aqueous NaOH was added into the reaction mixture until pH 8–9. The layers were separated and the organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the crude product which was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 2 : 5), which gave the title compound **11** as a pale brown gummy liquid (0.477 g, 95%).

IR (ν_{max}/cm^{-1}) 3584, 3392, 2921, 1589, 1449, 1219. δ_H (DMSO-d_6, 400 MHz) 3.90 (s, 3H), 3.95 (s, 3H), 4.52 (d, J = 5.4 Hz, 2H), 5.23 (t, J = 5.9 Hz, 1H), 6.38 (t, J = 6.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 7.12–7.21 (m, 2H), 7.37 (t, J = 7.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 8.09 (d, J = 7.4 Hz, 1H) and 11.41 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 55.7, 59.7, 61.0, 85.1, 106.9, 111.1, 111.3, 116.1, 118.3, 119.0, 120.5, 120.7, 121.9, 125.2, 129.7, 130.2, 138.6, 139.6, 142.1, 146.8 and 147.4. LRMS (ESI): m/z = 457 (M − H)$^+$. 240 (M − iodoaniline). HRMS (ESI) calcd for $C_{21}H_{18}IN_2O_2$ (M − H)$^+$: 457.0413, found: 457.0417.

Procedure for *N*-((1,4-dimethoxy-9*H*-carbazol-3-yl)methyl)-*N*-(2-iodophenyl)acetamide (12)

A round bottomed flask was charged with *N*-((1,4-dimethoxy-9*H*-carbazol-3-yl)methyl)-2-iodoaniline (**11**) (0.41 g, 0.89 mmol) and triethylamine (0.135 g, 1.33 mmol) in dichloromethane (5 mL) and cooled to below 5 °C. Freshly distilled acetyl chloride was slowly added (0.084 g, 1.07 mmol). The reaction was stirred at room temperature for 2 hours. After completion of the reaction, ice cold water was added into the reaction mixture and extracted with 3 × 20 mL of dichloromethane. The organic layer was washed with brine, and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the crude product which was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 0.5 : 10) to give the title compound **12** as a pale yellow gummy liquid (0.423 g, 94%).

IR (ν_{max}/cm^{-1}) 3778, 3584, 3469, 2401, 1648, 1470, 1305, 1215. δ_H ($CDCl_3$, 400 MHz) 1.87 (s, 3H), 3.54 (s, 3H), 3.94 (s, 3H), 4.52 (d, J = 14.2 Hz, 1H), 5.71 (d, J = 14.2 Hz, 1H), 6.69 (dd, J = 7.8 Hz, 1H), 6.92 (s, 1H), 6.95 (t, J = 7.8 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.37–7.45 (m, 2H), 7.91 (dd, J = 7.8 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H) and 8.32 (s, 1H). δ_C ($CDCl_3$ 100 MHz) 23.0, 44.7, 54.9, 56.0, 100.4, 108.3, 110.8, 119.5, 119.8, 121.9, 122.6 (2C), 125.4 (2C), 129.2, 130.7 (2C), 138.9, 140.0, 144.4, 147.1, 154.3 and 170.4. LRMS (ESI): m/z = 501 (M + H)$^+$. HRMS (ESI) calcd for $C_{23}H_{22}IN_2O_3$ (M + H)$^+$: 501.0675, found: 501.0696.

Preparation of *N*-(2-bromophenyl)-4-(((2-iodophenyl)amino)-methyl)-2,5-dimethoxyaniline (14)

A round bottomed flask was charged with 2-iodoaniline (**10**) (0.358 g, 1.5 mmol) and 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (**5b**) (0.5 g, 1.5 mmol) followed by i-PrOAc (10 mL) and trifluoroacetic acid (0.339 g, 3 mmol). Sodium triacetoxyborohydride (0.630 g, 3 mmol) was added as a solid over 2 min (exothermicity was observed up to ~40 °C). After 10 min agitation TLC showed the completion of the reaction. The reaction mixture was diluted with ethyl acetate (30 mL). A solution of 2 wt% of aqueous NaOH was added into the reaction mixture until pH 8–9. The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 2 : 5) to give the title compound **14** as a dark brown gummy liquid (0.764 g, 95%).

IR (ν_{max}/cm^{-1}) 3584, 3393, 3019, 2918, 1588, 1456, 1217. δ_H (DMSO-d_6, 400 MHz) 3.69 (s, 3H), 3.77 (s, 3H), 4.31 (d, J = 5.9 Hz, 2H), 5.20 (t, J = 5.9 Hz, 1H), 6.39 (t, J = 7.8 Hz, 1H), 6.63 (t, J = 7.8 Hz, 1H), 6.69 (s, 1H), 6.79 (t, J = 7.4 Hz, 1H), 6.86 (s, 1H), 7.02 (s, 1H), 7.10–7.17 (m, 2H), 7.24 (t, J = 7.8 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H) and 7.63 (d, J = 7.9 Hz, 1H). δ_C (DMSO-d_6, 100 MHz) 42.3, 55.9, 56.2, 85.2, 103.3, 111.2, 112.3, 112.9, 116.9, 118.3, 120.1, 121.3, 128.5, 129.3, 130.0, 132.7, 138.7, 140.9, 143.8, 147.3 and 151.1. LRMS (ESI): m/z = 537, 538, 539, 540, 541 (M + H)$^+$. HRMS (ESI) calcd for $C_{21}H_{21}BrIN_2O_2$ (M + H)$^+$: 538.9831, found: 538.9850.

Preparation of *N*-(4-((2-bromophenyl)amino)-2,5-dimethoxybenzyl)-*N*-(2-iodophenyl)acetamide (4)

A round bottomed flask was charged with *N*-(2-bromophenyl)-4-(((2-iodophenyl)amino)methyl)-2,5-dimethoxyaniline (**14**) (0.5 g, 0.92 mmol) and triethylamine (0.141 g, 0.14 mmol) in dichloromethane (20 mL) and cooled to below 5 °C. Freshly distilled acetyl chloride was slowly added (0.088 g, 1.1 mmol). The reaction was stirred at room temperature for 2 hours. After the completion of the reaction, ice cold water was added into the reaction mixture and extracted with 3 × 30 mL of dichloromethane and the organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford the crude product which was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 0.5 : 10) to give the title compound **4** as a brown gummy liquid (0.505 g, 94%).

IR (ν_{max}/cm^{-1}) 3778, 3399, 3019, 2400, 1648, 1524, 1215. δ_H (DMSO-d_6, 400 MHz) 1.71 (s, 3H), 3.40 (s, 3H), 3.71 (s, 3H), 4.29 (d, J = 14.2 Hz, 1H), 5.13 (d, J = 14.2 Hz, 1H), 6.54 (s, 1H), 6.68 (s, 1H), 6.73–6.79 (m, 1H), 6.81 (s, 1H), 7.02 (d, J = 6.4 Hz, 1H), 7.05–7.11 (m, 2H), 7.23 (t, J = 8.3 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H) and 7.96 (d, J = 7.8 Hz, 1H). δ_C (DMSO-d_6, 100 MHz) 22.7, 44.8, 55.7, 56.2, 101.2, 102.9, 112.6, 114.3, 117.2, 117.5, 121.5, 128.4, 129.2, 129.8, 130.6, 130.7, 132.8, 139.4, 140.8, 143.5, 144.2, 151.5 and 168.8. LRMS (ESI): m/z = 579.9, 580.9, 582.99, 583.99 (M + H)$^+$. HRMS (ESI) calcd for $C_{23}H_{23}N_2O_3BrI$ (M + H)$^+$: 580.9937, Found: 580.9914

Preparation of 1-(7,13-dimethoxy-6,12-dihydro-5*H*-indolo-[3,2-*j*]phenanthridin-5-yl)ethanone (13)

From *N*-((1,4-dimethoxy-9*H*-carbazol-3-yl)methyl)-*N*-(2-iodophenyl)acetamide (12). To a solution of *N*-((1,4-dimethoxy-9*H*-carbazol-3-yl)methyl)-*N*-(2-iodophenyl)acetamide (**12**) (0.2 g, 0.4 mmol) in degassed dry DMF (6 mL), PCy_3 (0.025 g,

0.08 mmol), anhydrous powdered K_2CO_3 (0.110 g, 0.8 mol) and $Pd(OAc)_2$ (0.005 g, 0.02 mmol) were added. The reaction mixture was stirred at 110 °C under argon atmosphere for 10 hours (the reaction was monitored by TLC). The reaction mixture was cooled to room temperature and filtered over a celite bed and washed with EtOAc (10 mL). The combined organic layer was concentrated under reduced pressure to yield the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 2.5 : 5) which gave the desired compound as a brown solid **13** (1.034 g, 90%).

From *N*-(4-((2-bromophenyl)amino)-2,5-dimethoxybenzyl)-*N*-(2-iodophenyl)acetamide (4). To a solution of *N*-(4-((2-bromophenyl)amino)-2,5-dimethoxybenzyl)-*N*-(2-iodophenyl)acetamide (**4**) (0.5 g, 0.86 mmol) in degassed dry DMF (6 mL), PCy_3 (0.072 g, 0.25), JohnPhos (0.025 g, 0.08 mmol), anhydrous powdered K_2CO_3 (0.475 g, 3.5 mmol) and $Pd(OAc)_2$ (0.010 g, 0.04 mmol) were added. The reaction mixture was stirred at 110 °C under argon atmosphere for 10 hours (the reaction was monitored by TLC). The reaction mixture was cooled to room temperature and filtered over a celite bed and washed with EtOAc (10 mL). The combined organic layer was concentrated under reduced pressure to yield the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 2.5 : 5) which gave the desired compound as a brown solid **13** (0.280 g, 88%).

Mp: 239–241 °C. IR (ν_{max}/cm^{-1}) 3231, 2837, 1734, 1638, 1624, 1396. δ_H (DMSO-d_6, 400 MHz) 2.11 (s, 3H), 3.82 (s, 3H), 3.98 (s, 3H), 4.5–5.2 (b, 2H), 7.23 (t, J = 7.7 Hz, 1H), 7.41–7.46 (m, 3H), 7.55 (d, J = 8.0 Hz, 2H), 8.11 (d, J = 7.7 Hz, 1H), 8.46 (m, 1H) and 11.59 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 22.0, 60.3, 61.0, 111.3 (2C), 116.3, 119.4 (2C), 120.7 (2C), 122.0 (2C), 125.0 (2C), 125.9, 127.7, 134.0, 138.5, 139.4, 140.2, 146.4 and 168.2. LRMS (ESI): m/z = 373 $(M + H)^+$. HRMS (ESI) calcd for $C_{23}H_{21}N_2O_3$ $(M + H)^+$: 373.1552, found: 373.1548

Preparation of calothrixin B (2)

To a stirred solution of compound **13** (0.2 g, 0.54 mmol) in acetonitrile (5 mL) and water (5 mL), ceric ammonium nitrate (CAN) (0.740 g, 1.35 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, water (20 mL) was added into the reaction mixture and extracted with EtOAc (3 × 20 mL). The organic layer was concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 0.4 : 10) which afforded red calothrixin B (**2**) (0.137 g, 85%).

Mp: >300 °C.[4] IR (ν_{max}/cm^{-1}) 3863, 3404, 3019, 2905, 2834, 1720, 1602, 1426, 1215. δ_H (DMSO-d_6, 400 MHz) 7.40 (t, J = 7.8 Hz, 1H), 7.48 (t, J = 8.3 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.89 (t, J = 8.3 Hz, 1H), 7.95 (t, J = 8.3 Hz, 1H), 8.16–8.19 (m, 2H), 9.58 (d, J = 8.3 Hz, 1H), 9.63 (s, 1H) and 13.17 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 113.9, 115.5, 122.3, 122.6, 123.3, 124.4, 124.9, 127.2 (2C), 129.8, 130.3, 131.6, 132.7, 138.0, 138.4, 147.5, 151.2, 180.4 and 180.9. LRMS (ESI): m/z = 299 $(M + H)^+$. HRMS (ESI) calcd for $C_{19}H_{11}N_2O_2$ $(M + H)^+$: 299.0821, found: 299.0811.

Preparation of 1,4-dimethoxy-3-methyl-9*H*-carbazole (15)

A round bottomed flask was charged with triethylsilane (0.683 g, 5.8 mmol) and trimethylsilyl chloride (0.532 g, 4.9 mmol) under a nitrogen atmosphere. Then a solution of 1,4-dimethoxy-9*H*-carbazole-3-carbaldehyde (**9**) (0.5 g, 1.9 mmol) in acetonitrile (5 mL) was added slowly at room temperature and stirred for 4 hours. After completion of the reaction, water (10 mL) was added and the volatiles were removed under vacuum. The reaction mixture was extracted with 3 × 20 mL of EtOAc and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 0.5 : 5) which gave the title compound **15** as an orange solid (0.393 g, 83%).

Mp: 99–101 °C [19] (reported 98–100 °C). IR (ν_{max}/cm^{-1}) 3863, 3404, 3019, 2905, 2834, 1720, 1602, 1426, 1215. δ_H ($CDCl_3$, 400 MHz) 2.37 (s, 3H), 3.88 (s, 6H), 6.61 (s, 1H), 7.15 (ddd, J = 6.9 and 2.0 Hz, 1H), 7.31 (m, 2H) and 8.14 (d, J = 7.8 Hz, 2H). δ_C ($CDCl_3$, 100 MHz) 15.4, 55.8, 60.2, 108.8, 110.6, 117.3, 119.5, 120.1, 122.0, 122.6, 125.3, 129.3, 139.1, 141.7 and 147.1. LRMS (ESI): m/z = 242 $(M + H)^+$. HRMS (ESI) calcd for $C_{15}H_{16}NO_2$ $(M + H)^+$: 242.1181, found: 242.1175.

Preparation of *N*-(2-bromophenyl)-2,5-dimethoxy-4-methylaniline (16)

A round bottomed flask was charged with triethylsilane (1.01 g, 8.7 mmol) and trimethylsilyl chloride (0.793 g, 7.3 mmol) under a nitrogen atmosphere. Then a solution of 4-((2-bromophenyl)amino)-2,5-dimethoxybenzaldehyde (**5b**) (1 g, 2.9 mmol) in acetonitrile (10 mL) was added slowly at room temperature and stirred for 6 hours. After completion of the reaction, water (10 mL) was added and the volatiles were removed under vacuum. The mixture was extracted with 3 × 20 mL of EtOAc and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 1 : 10) which gave the title compound **16** as a light brown gummy liquid (0.770 g, 80%).

IR (ν_{max}/cm^{-1}) 3863, 3404, 3019, 2905, 2834, 1720, 1602, 1426, 1215. δ_H (DMSO-d_6, 400 MHz) 2.09 (s, 3H), 3.69 (s, 3H), 3.74 (s, 3H), 6.59 (s, 1H), 6.74 (t, J = 7.8 Hz, 1H), 6.81 (s, 1H), 6.91 (s, 1H), 6.99 (d, J = 8.3 Hz, 1H), 7.20 (t, J = 8.3 Hz, 1H) and 7.54 (d, J = 7.8 Hz, 1H). δ_C ($CDCl_3$, 100 MHz) 15.9, 56.2, 56.5, 103.3, 112.6 and 114.5, 115.5, 120.1, 120.6, 128.0, 128.9, 133.0, 141.6, 144.1, 151.5. LRMS (ESI): m/z = 322, 324 $(M + H)^+$. HRMS (ESI) calcd for $C_{15}H_{17}BrNO_2$ $(M + H)^+$: 322.0443, found: 322.0435.

Preparation of 2-((2-bromophenyl)amino)-5-methylcyclohexa-2,5-diene-1,4-dione (17)

To a stirred solution of *N*-(2-bromophenyl)-2,5-dimethoxy-4-methylaniline (**16**) (0.7 g, 2.2 mol) in acetonitrile (15 mL) and water (15 mL), CAN (3 g, 5.4 mol) was added. The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, water (40 mL) was added into the reaction mixture and extracted with EtOAc (3 × 30 mL). The organic layer was concentrated under reduced pressure to give the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 0.2 : 10) which afforded the red title compound (0.559 g, 88%).

Mp 231–233 °C. IR (ν_{max}/cm^{-1}) 3434, 3306, 2954, 2919, 2346, 1735, 1670, 1530, 1223. δ_H (DMSO-d_6, 400 MHz) 1.97 (s, 3H), 5.24 (s, 1H), 6.72 (s, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H) and 8.71 (s, 1H). δ_C (DMSO-d_6, 100 MHz) 16.3, 101.8, 117.4, 122.7, 126.2, 128.3, 129.5, 133.5, 135.8, 142.3, 149.3, 183.3 and 186.8. LRMS (ESI): m/z = 291.9, 293.9 $(M + H)^+$. HRMS (ESI) calcd for $C_{13}H_{11}BrNO_2$ $(M + H)^+$: 291.9973, found: 291.9968.

Preparation of murrayaquinone A (3)

From 1,4-dimethoxy-3-methyl-9*H*-carbazole (15). A solution of 1,4-dimethoxy-3-methyl-9*H*-carbazole (**15**) (0.3 g, 1.2 mmol) in dichloromethane (5 mL) was cooled to −78 °C. Boron tribromide in dichloromethane (1 M; 2.5 mL, 2.4 mmol) was added at −78 °C and the mixture was stirred for 22 hours at room temperature under air. The reaction mixture was then poured into ice–water (10 mL) and the product was extracted into EtOAc (3 × 20 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 1 : 5) which afforded the red title compound (0.194 g, 74%).

From 2-((2-bromophenyl)amino)-5-methylcyclohexa-2,5-diene-1,4-dione (17). A mixture of 2-((2-bromophenyl) amino)-5-methylcyclohexa-2,5-diene-1,4-dione (**17**) (0.1 g, 0.34 mmol), anhydrous powdered K_2CO_3 (0.094 g, 0.68 mmol), palladium(II) acetate (0.038 g, 0.02 mmol), tricyclohexylphosphine (0.019 g, 0.07 mmol) and 10 mol% of JohnPhos (0.010 g, 0.03 mol) in acetonitrile (5 mL) was heated to 110 °C under argon atmosphere for 9 hours. The reaction mixture was filtered over a celite bed and washed with EtOAc. The combined organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc–petroleum ether = 1 : 5) which gave the red title compound **3** (0.064 g, 88% yield).

Mp: 240–242 °C (reported[12] 246–247 °C). IR (ν_{max}/cm^{-1}) 3863, 3404, 3019, 2905, 2834, 1720, 1602, 1426, 1215. δ_H ($CDCl_3$, 400 MHz) 2.18 (d, J = 1.5 Hz, 3H), 6.52 (s, 1H), 7.33–7.45 (m, 2H), 7.48 (d, J = 8.3 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H) and 9.18 (br s, 1H). δ_C ($CDCl_3$ + DMSO-d_6 100 MHz) 20.9, 118.8, 120.7, 126.7, 128.6, 128.8, 131.0, 136.6, 141.0, 142.7, 153.0, 185.1 and 188.1. LRMS (ESI): m/z = 212 $(M + H)^+$.

Acknowledgements

The authors would like to thank Dr Vilas H. Dahanukar for his constant encouragement and support. We also thank the analytical department of Dr Reddy's Laboratories, for providing analytical support.

Notes and references

1 R. W. Rickards, J. M. Rothschild, A. C. Willis, N. M. de Chazal, J. Kirk, K. Kirk, K. J. Saliba and G. D. Smith, *Tetrahedron*, 1999, **55**, 13513.
2 P. H. Bernardo, C. L. L. Chai, G. A. Heath, P. J. Mahon, G. D. Smith, P. A. Warning and B. A. Wilkes, *J. Med. Chem.*, 2004, **47**, 4958.
3 Q. A. Khan, J. Lu and S. M. Hecht, *J. Nat. Prod.*, 2009, **72**, 438.
4 T. R. Kelly, Y. Zhao, M. Cavero and M. Torneiro, *Org. Lett.*, 2000, **2**, 3735.
5 D. Sissouma, S. C. Collet and A. Y. Guingant, *Synlett*, 2004, 2612.
6 (*a*) P. H. Bernardo and C. L. L. Chai, *J. Org. Chem.*, 2003, **68**, 8906; (*b*) N. Ramkumar and R. Nagarajan, *J. Org. Chem.*, 2014, **79**, 736.
7 (*a*) T. Abe, T. Ikeda, R. Yanada and M. Ishikura, *Org. Lett.*, 2011, **13**, 3356; (*b*) T. Abe, T. Ikeda, T. Choshi, S. Hibino, N. Hatae, E. Toyata, R. Yanada and M. Ishikura, *Eur. J. Org. Chem.*, 2012, 5018.
8 N. Ramkumar and R. Nagarajan, *J. Org. Chem.*, 2013, **78**, 2802.
9 B. M. Ramalingam, V. Saravanan and A. K. Mohanakrishanan, *Org. Lett.*, 2013, **15**, 3726.
10 M.-L. Bennasar, T. Roca and F. Ferrando, *Org. Lett.*, 2006, **8**, 561–564.
11 (*a*) C. S. P. McErlean, J. Sperry, A. J. Blake and C. J. Moody, *Tetrahedron*, 2007, **63**, 10963; (*b*) A. Yamabuki, H. Fujinawa, T. Choshi, S. Tohyama, K. Matsumoto, K. Ohnuma, J. Nobuhiro and S. Hibino, *Tetrahedron Lett.*, 2006, **47**, 5859; (*c*) J. Sperry, C. S. P. McErlean, A. M. Z. Slawin and C. J. Moody, *Tetrahedron Lett.*, 2007, **48**, 231.
12 T. S. Wu, T. Ohta and H. Furukawa, *Heterocycles*, 1983, **20**, 1267.
13 (*a*) L. F. Tietze and A. Dufrt, *Pure Appl. Chem.*, 2010, **82**, 1375; (*b*) R. T. Ruck, M. A. Huffman, M. M. Kim, M. Shevlin, W. V. Kandur and I. W. Davies, *Angew. Chem., Int. Ed.*, 2008, **47**, 4711; (*c*) L. F. Tietze, T. Nobel and M. Spescha, *J. Am. Chem. Soc.*, 1998, **120**, 8971.
14 A. de Meijere and F. E. Meier, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2379.
15 B. A. Hathaway, B. E. Taylor and J. S. Wittenbom, *Synth. Commun.*, 1998, **28**, 4629.
16 (*a*) M. R. Biscoe, B. P. Fors and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 6686; (*b*) J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1144; (*c*) B. Schlummer and U. Scholz, *Adv. Synth. Catal.*, 2004,

346, 1599; (*d*) M. R. Biscoe, B. T. Fors and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 6686; (*e*) A. W. Schmidt, K. R. Reddy and H.-J. Knölker, *Chem. Rev.*, 2012, **112**, 3193.
17 M. McLaughlin, M. Palucki and I. W. Davies, *Org. Lett.*, 2006, **8**, 3307.
18 (*a*) S. M. Bhosale, R. L. Gawade, V. G. Puranik and R. S. Kusurkar, *Tetrahedron Lett.*, 2012, **53**, 2894; (*b*) S. M. Bhosale, A. A. Momin, S. Kunjir, P. R. Rajamohanan and R. S. Kusurkar, *Tetrahedron Lett.*, 2014, **55**, 155.
19 R. B. Bedford, J. G. Bowen and A. L. Weeks, *Tetrahedron Lett.*, 2013, **69**, 4389.
20 T. Martin and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1988, 235.