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Reactions of 2-naphthylphenylacetylenes and 2-naphthylbenzaldehyde *O*-phenyl oximes. A synthesis of the angucycline tetrangulol and 1,10,12-trimethoxy-8-methylbenzo[*c*]phenanthridine

Kennedy J. Ngwira,[a] Amanda L. Rousseau,[a] Myron M. Johnson[a] and Charles B. de Koning*[a]

Abstract: The Suzuki-Miyaura coupling reaction between 1,4,5-(trimethoxynaphthalen-2-yl)boronic acid and 2-iodo-3-methoxy-5-methylbenzaldehyde afforded intermediate, 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde. Conversion of this benzaldehyde into the alkyne, 2-(2-ethynyl-6-methoxy-4-methylphenyl)-1,4,5-trimethoxynaphthalene was accomplished utilizing the Corey-Fuchs reaction. Exposure of the derived acetylene to a catalytic platinum(II)-mediated ring closure yielded the required tetracyclic aromatic product, 1,7,8,12-tetramethoxy-3-methyltetraphene which was converted into tetrangulol. Exposure of the related 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde *O*-phenyl oxime to microwave irradiation in an ionic liquid yielded 1,10,12-trimethoxy-8-methylbenzo[*c*]phenanthridine, instead of the desired natural product phenanthroviridone.

Introduction

The angucyclines are a large group of naturally occurring quinones that display a wide range of biological activities, including anticancer and antibacterial activity.[1] Examples include the aromatic quinone tetrangulol **1** or the more complex quinone aquayamycin **2** (**Figure 1**). The biosynthetically related[2] complex natural products jadomycin A **3** and jadomycin Y **4** also exhibit interesting biological properties.[3-7] The simpler benzo[*b*]phenanthridine skeleton is found in the natural product phenanthroviridone **5**, which displays anticancer activities.[8]

As a result of their biological activity and interesting structures, many methods have been developed for the synthesis of angucyclines. The first synthesis of tetrangulol was developed in 1976,[9] however since then, a variety of other methods have been reported with a number of them involving the Diels-Alder reaction as a key step.[10,11,12] Other methods involve carbonyl condensation chemistry in key steps[13-15] while Kraus[16] has taken advantage of an interesting base mediated ring closure in a key step of his synthesis. Phenanthroviridone **5** has been synthesized by Gould,[17] Echavarren[18] and Snieckus,[19] while model studies towards their synthesis were conducted by Valderrama.[20]

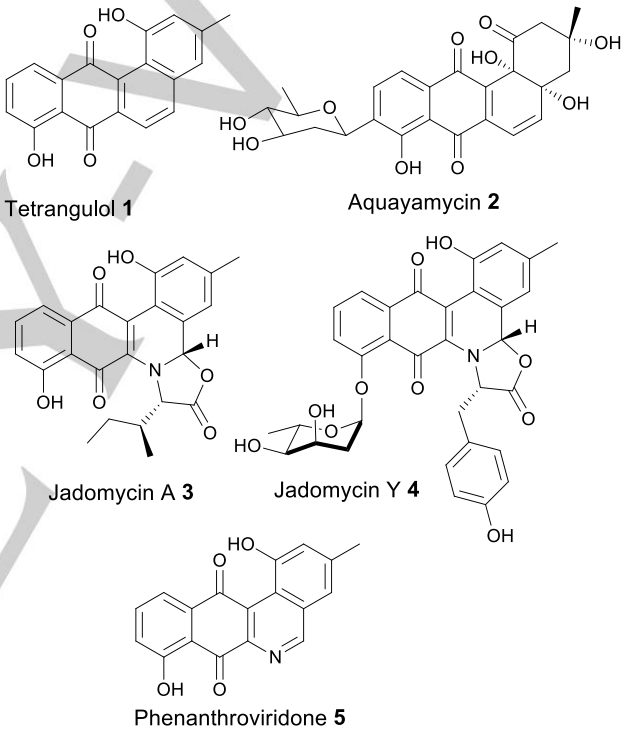

Figure 1. Naturally occurring angucyclines and benzo[*b*]phenanthridines

As part of our programme on the synthesis of aromatic and heteroaromatic compounds,[21] we report here on our results leading to the synthesis of tetrangulol **1**. The key final aromatic ring forming reaction takes place by exposure of 2-naphthylphenylacetylenes to platinum(II) chloride or gold(III) chloride. Secondly, we outline our attempts to use UV light and microwave methodology to synthesize the natural product phenanthroviridone **5**, from the related 2-naphthylbenzaldehyde *O*-phenyl oximes and how this resulted in the formation of the undesired benzo[*c*]phenanthridine, 1,10,12-trimethoxy-8-methylbenzo[*c*]phenanthridine.

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Results and Discussion

Previously in our laboratories, we have used the ring-closing metathesis (RCM) reaction as a key step in the assembly of carbazoles.[22] We thought that our first target compound, tetrangulol **1**, could be synthesized utilizing this approach starting from a suitably substituted *bis*-styrene such as **6** (**Figure 2**). Further disconnection would lead to the naphthalene boronic acid **7** (which could be prepared from bromonaphthalene **8**) with the Suzuki- Miyaura coupling partner being the benzaldehyde **9**.

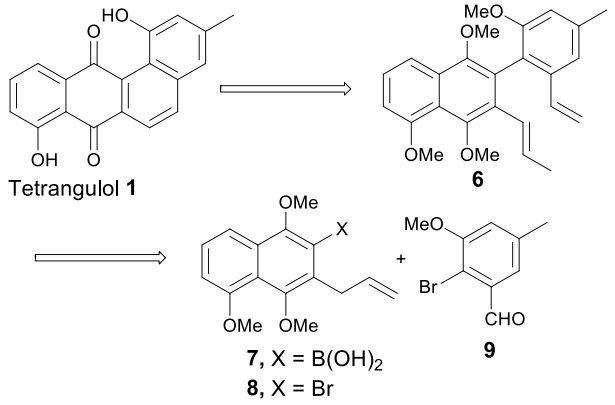
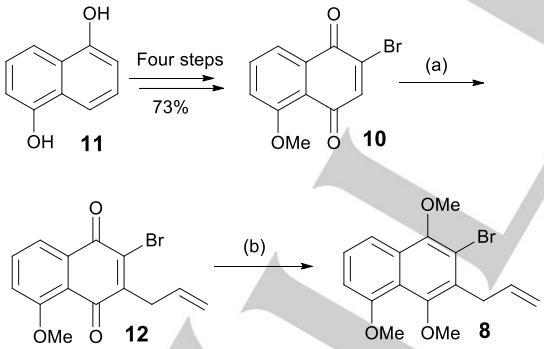


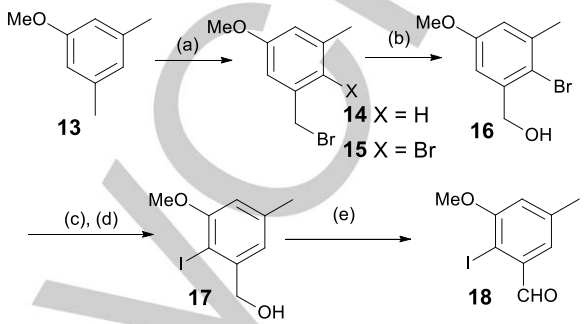
Figure 2. Retrosynthesis of Tetrangulol **1**

2-Bromo-5-methoxy-1,4-naphthoquinone **10** was synthesized in 4 steps from 1,5-dihydroxynaphthalene **11** in an overall yield of 73% using previously reported methodology.[23] When **10** was treated with vinyl acetic acid, in the presence of silver nitrate as detailed by Asao,[24] this furnished the desired 3-allyl substituted naphthoquinone **12** (**Scheme 1**). Reduction of the quinone of **12** followed by protection as the *O*-dimethyl ether[25] afforded the desired compound **8**.



Scheme 1. *Reagents and Conditions*: (a) (i) vinyl acetic acid, $AgNO_3$, MeCN, 65 °C, (ii) $(NH_4)_2S_2O_8$, H_2O, 16 h, 65 °C, 72%; (b) $Na_2S_2O_4$, TBAI, KOH, Me_2SO_4, THF-H_2O, r.t., 18 h, 75%.

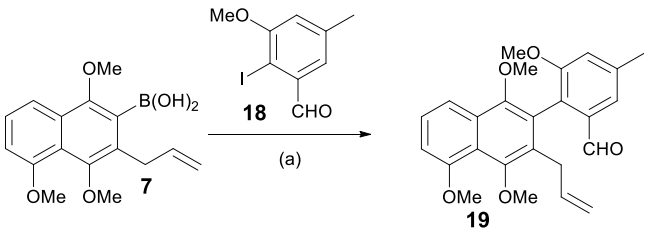
Next we set about the synthesis of bromobenzaldehyde **9**. However, in our hands all attempts to convert 3,5-dimethylanisole **13** to 1-(bromomethyl)-3-methoxy-5-methylbenzene **14** as reported in the literature by Kamikawa[26] and Takahashi[27] were unsuccessful. It appeared (as also described by Bickelhaupt)[28] that under the radical conditions utilized for bromination by Kamikawa and Takahashi that nuclear aromatic bromination took place initially and *only* on the addition of *two* mole equivalents was the dibrominated anisole **15** containing a benzylic bromine furnished (**Scheme 2**). Initially carbon tetrachloride was utilized as a solvent in the reaction. However, we were also able to replace this solvent with ethyl acetate[29] and microwave irradiation to effect the same transformation.



Scheme 2. *Reagents and Conditions*: (a) (i) NBS, benzoyl peroxide, CCl_4, r.t.; or (ii) NBS, benzoyl peroxide, EtOAc, microwave (300W), reflux; (b) $CaCO_3$, dioxane/H_2O, reflux. For CCl_4, method, 70% over 2 steps; for EtOAc method 72% over 2 steps; (c) *n*-BuLi, THF, -78 °C, 94%; (d) (i) *n*-BuLi, Et_2O, -78 °C; (ii) I_2 in THF, 0 °C, 65%; (e) MnO_2, CH_2Cl_2, 98%.

Using this methodology we could make gram quantities of **15**. The benzyl bromide could easily be converted into the benzyl alcohol **16** by using a mixture of dioxane and water in the presence of calcium carbonate, rather than using the Hass procedure to afford the related benzaldehyde as described in the literature.[30] Lithiation of **16** followed by aqueous work-up allowed for the removal of the aromatic bromine. This compound was isolated and under the conditions developed by Takahashi[27] was exposed to further *n*-BuLi in Et_2O and then treated with iodine, which allowed for the exclusive formation of **17**. This was readily oxidized to the desired substituted benzaldehyde **18**.

The next step entailed the Suzuki-Miyaura cross-coupling reaction between benzaldehyde **18** and the naphthalene boronic acid **7**, which was synthesized from the previously prepared bromonaphthalene **8**. Disappointingly, very low yields of the desired biaryl compound **19** (**Scheme 3**) were obtained, presumably as a tetra-substituted biaryl axis is being formed.



Scheme 3. *Reagents and Conditions*: (a) cat. $Pd(PPh_3)_4$, aq. Na_2CO_3, DME, reflux, 12%.

We therefore adopted an alternative strategy. Further retrosynthetic analysis of tetrangulol **1** led us to the biaryl intermediate **20** (**Figure 3**). In order to complete the synthesis from this intermediate an extra carbon atom would have to be introduced in order to form the last aromatic ring of tetrangulol. Further disconnection led us to the naphthalene boronic acid **21** lacking the 3-allyl substituent and the same benzaldehyde, 2-iodo-3-methoxy-5-methylbromobenzaldehyde **18** that we had previously synthesized.

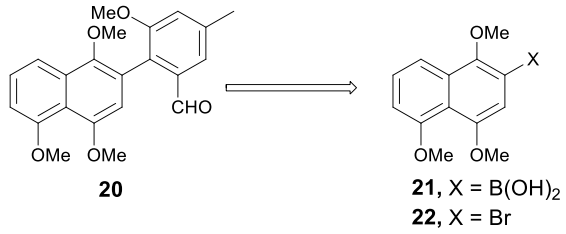
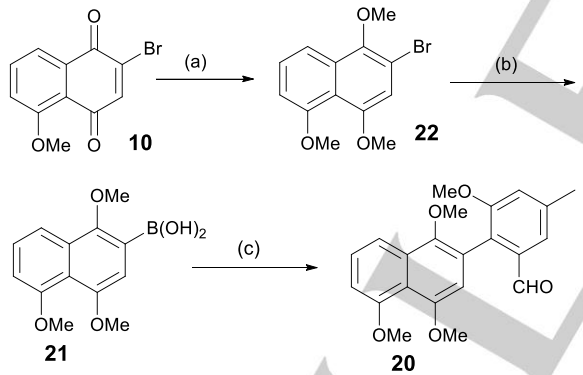


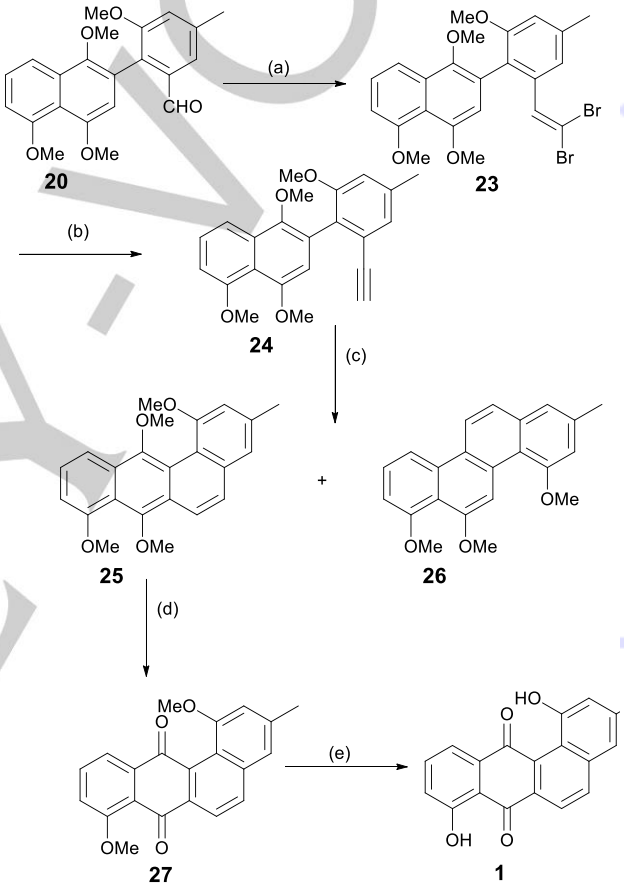
Figure 3. Retrosynthesis of Tetrangulol **1**

The synthesis of 2-bromo-1,4,5-trimethoxynaphthalene **22** has been reported in the literature. [23] Conversion of **10** to **22** was accomplished utilizing a reductive methylation procedure[25] in good yields (**Scheme 4**). When **22** was subjected to *n*-BuLi and then triisopropylborate, followed by work up with dilute acid yielded the desired boronic acid **21** needed for the Suzuki-Miyaura coupling reaction. Treatment of **21** with bromobenzaldehyde **18** under palladium catalysis conditions afforded the desired naphthalene, 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde **20**, in good yields.



Scheme 4. *Reagents and Conditions*: (a) $Na_2S_2O_4$, TBAI, KOH, Me_2SO_4, THF-H_2O, r.t., 18 h, 79%; (b) *n*-BuLi, $B(O^iPr)_3$, THF, -78 °C; (c) **18**, cat. $Pd(PPh_3)_4$, aq. Na_2CO_3, DME, reflux, 80%.

Alkynes have been used extensively by Fürstner[31a] and Echavarren[31b] for the construction of rings, including aromatic rings either using gold(III) or platinum(II) catalysis. Significantly, the application of the platinum-mediated methodology has been used to assemble angularly fused polycyclic aromatic hydrocarbons.[31a] [32] In our case, application of the Corey-Fuchs reaction allowed for the facile transformation of benzaldehyde **20** to alkyne **24** *via* **23**, in good yields (**Scheme 5**). Next was the key step, the formation of the final aromatic ring of the tetrangulol skeleton. Exposure of **24** to catalytic platinum(II) chloride resulted in the formation of the desired tetracyclic product **25** in a yield of 61%. Evidence was provided by the ^{1}H NMR spectrum where the aromatic protons for the newly formed aromatic ring were found at δ 8.03 (d, J = 9.2 Hz) and δ 7.36 (d, J = 9.2 Hz). In the reaction, surprisingly a second aromatic product was also formed in 23% yield which was identified as 1,10,12-trimethoxy-8-methylchrysene **26**. The two products were easily separable by silica gel chromatography. When gold(III) chloride was used as the catalyst the same two aromatic products **25** and **26** were formed from **20** in yields of 56% and 31% respectively.



Scheme 5. *Reagents and Conditions*: (a) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 90%; (b) *n*-BuLi, THF, -78 °C, 88%; (c) cat. $PtCl_2$, PhMe, 90 °C, 61% **25** and 23% **26** or cat. $AuCl_3$, PhMe, 90 °C, 56% **25** and 31% **26**; (d) CAN, MeCN/H_2O, 86% (e) [11]BBr_3, CH_2Cl_2, -78 °C.

Examination of the literature[31a][33] led us to speculate that the desired product **25** would be formed by initial formation of the η^2 complex **I** (**Figure 4**). The complex could then undergo a „Friedel-Crafts"-type reaction to yield **II** by means of a 6-*endo* dig cyclization, which would ultimately lead to **25**. In an analoguos manner, **26** would be formed by the related „Friedel-Crafts"-type reaction to furnish **III**. After explusion of a methoxy anion intermediate **IV** would be formed, which would aromatize to afford **26**.

Alternatively, the vinylidene complex **V** could be formed from **I** which then undergoes a 6π–electrocyclization to form the new aromatic ring **VI**, allowing for the formation of **25** (**Figure 5**). In a similar manner, the 6π–electrocyclization on **VII** would result in **VIII**, which after expulsion of a methoxy anion would yield **26**.

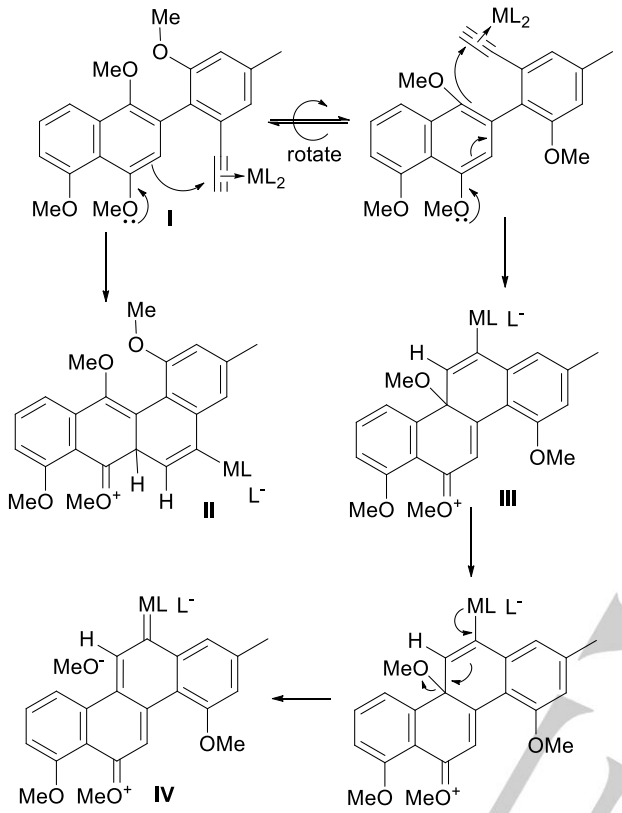


Figure 4. Plausible mechanism for the formation of **25** and **26**

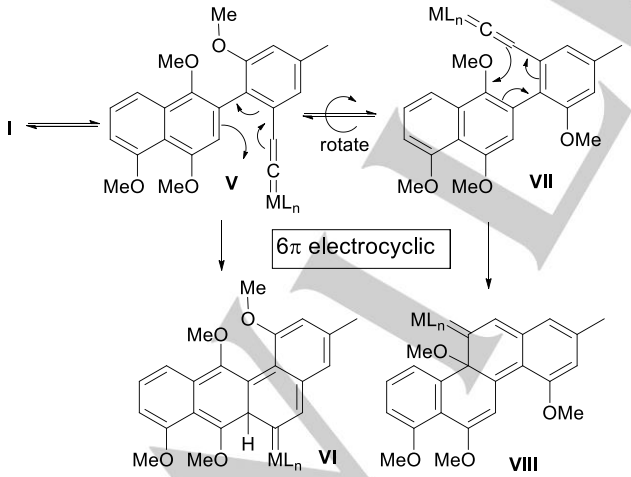


Figure 5. Alternative plausible mechanism for the formation of **25** and **26**

Compound **25** was subjected to CAN oxidation to afford the quinone **27** (**Scheme 5**). The synthesis of quinone **27** represents a formal synthesis of tetrangulol **1** as **27** has been treated with boron tribromide to yield tetrangulol **1** in 97% yield.[11] In our hands this reaction proceeded to afford tetrangulol **1** in good yield together with a minor unidentified impurity.

Using this methodology we believed it would be possible to synthesize phenanthroviridone **5**, the nitrogen analog of tetrangulol, as long as the synthesis of the aromatic oxime **28** (**Figure 6**) could be accomplished. We anticipated that the oxime **28** could be synthesized from benzaldehyde **20**, which had been used in our synthesis of tetrangulol.

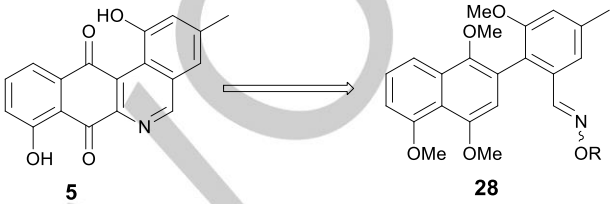
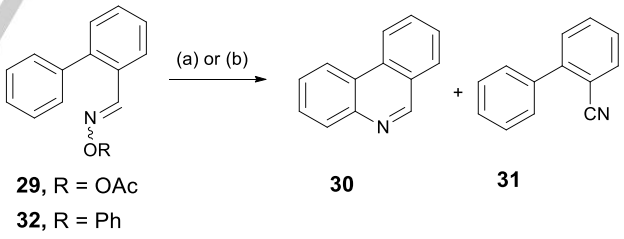


Figure 6. Retrosynthesis of phenanthroviridone **5**

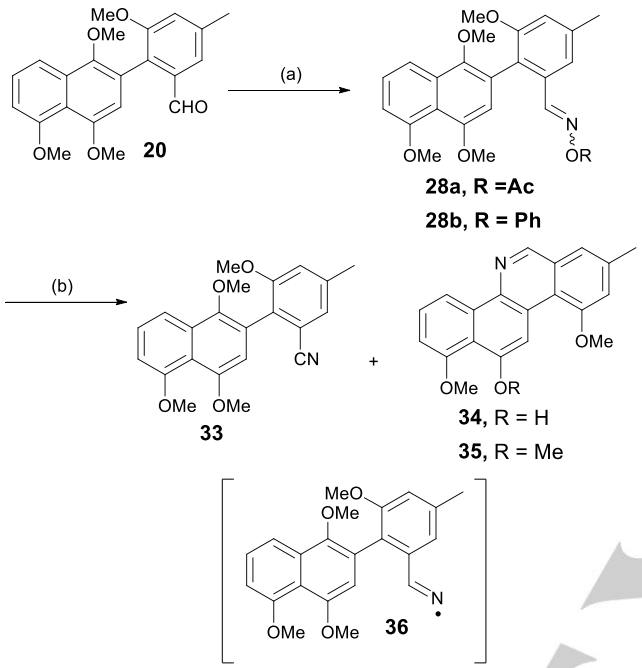
In the literature there are examples of the use of oximes, either as the oxime ether or as the oxime ester, leading to the formation of nitrogen heterocycles by intramolecular reactions of suitably substituted aromatic compounds, as shown in the two examples in **Scheme 6**. The first[34] is a light-induced cyclisation in which **29** leads to the formation of **30** as the major product and significant amounts of **31**. The second[35] uses microwave irradiation to afford exclusively **30** in good yield (76%) from the oxime ether **32**. Alternatively, the use of catalytic iron acetylacetonate in acetic acid can also be used to facilitate similar transformations.[36] A third procedure we also decided to investigate was the $Pd_2(dba)_3$ mediated method developed utilizing oxime esters by Hartwig,[37] also for the formation of carbon nitrogen bonds on an aromatic nucleus.



Scheme 6. *Reagents and Conditions*: (a) **29**, hγ, 400W mercury lamp, Pyrex, *t*-butanol, r.t., 58% **30**, 28% **31**; (b) **32**, microwave irradiation, $emimPF_4$, *t*-butanol, 30 min, 160 °C, 76%; **30**, 0% **31**. [33], [34]

The conversion of **20** to the oxime ethers **28a** and **28b** proceeded smoothly on exposure to either $NH_2OAc{\cdot}HCl$ or $NH_2OPh{\cdot}HCl$ (**Scheme 7**). Disappointingly, exposure of **28a** to $Pd_2(dba)_3$ under conditions developed by Hartwig only allowed for the formation of benzonitrile **33**. UV irradiation of **28a** in the presence of *t*-butanol afforded a product in which there were only three methoxy substituents in the ^1H NMR spectrum instead of the required four. It was clear from the ^1H NMR spectrum that two aromatic singlets at δ 9.15 and δ 8.87 were present, along with two broad singlets for the two *meta*-substituted aromatic singlets. Comparison of the ^1H NMR spectrum of the product

with that reported on the naphthol equivalent **34**,[19] disappointingly indicated that the undesired benzo[*c*]phenanthridine **35** had been synthesized (**Scheme 7**). Microwave irradiation of **28b** in the presence of one mole equivalent of the ionic liquid $EmimPF_6$ also afforded the same benzo[*c*]phenanthridine **35** together with small amounts of the benzonitrile **33**.



Scheme 7. *Reagents and Conditions*: (a) (i) NH_2OAc•HCl, pyridine, r.t., 86% **28a**; NH_2OPh•HCl, pyridine, r.t., 93%, **28b**; (b) **28a**, cat. $Pd_2(dba)_3$ toluene, $CsCO_3$, 150 °C, **33**, 62% (b) (i) **28a**, $EmimPF_6$, *t*-PhBu, microwave, 160 °C, **33** 11%, **35** 58%; Or (ii) **28b**, UV reactor, *t*-BuOH, **33** 18%, **35** 46%.

Presumably the benzo[*c*]phenanthridine **35** is formed *via* the formation of the iminyl radical **36** which results in addition to the naphthalene with the expulsion of a methoxy radical to regain aromaticity and form **35**. As opposed to the expulsion of a hydrogen radical that we had anticipated based on the cyclizations conducted using gold(III) or platinum(II) catalysis. While the synthesis of the benzo[*c*]phenanthridine nucleus was undesired this methodology may provide a novel route to access this class of natural products.[38]

Conclusions

Novel synthetic methodology has been developed for the synthesis of tetrangulol **1**. The synthesis of the key intermediate 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde **20** was accomplished utilizing the Suzuki-Miyaura coupling reaction of 1,4,5-trimethoxynaphthalen-2-yl)boronic acid **21** and 2-iodo-3-methoxy-5-methylbenzaldehyde **18**. The benzaldehyde **18** was prepared in five steps from 3,5-dimethylanisole in an overall yield of 43%, while the boronic acid **21** was prepared from 1,5-dihydroxynaphthalene in seven steps in an overall yield of 58%. Conversion of **20** into the desired alkyne, 2-(2-ethynyl-6-methoxy-4-methylphenyl)-1,4,5-trimethoxynaphthalene **24** was accomplished utilizing the Corey-Fuchs reaction. Exposure of **24** to a catalytic platinum(II) mediated ring closure afforded the required tetracyclic aromatic product **25** which was converted into tetrangulol **1**.

Attempted conversion of the intermediate 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde **20** to the nitrogen derivative of tetrangulol, phenanthroviridone **5**, by treatment of the oxime ethers **28a** or **28b** with microwave irradiation in the presence of the ionic liquid $EmimPF_6$ furnished the undesired benzo[*c*]phenanthridine, 1,10,12-trimethoxy-8-methylbenzo[*c*]phenanthridine **35**.

Experimental Section

Solvents utilized for chromatographic techniques (ethyl acetate and *n*-hexane) were distilled prior to use by means of conventional distillation processes. The solvents employed in reactions were first dried over the suitable drying agent, followed by distillation under an inert atmosphere (argon or nitrogen gas). Acetonitrile and dichloromethane were distilled over calcium hydride, whereas tetrahydrofuran was distilled over sodium with benzophenone as an indicator. Toluene was distilled over sodium. All the required chemicals or reagents were obtained from FLUKA, SIGMA ALDRICH or MERCK and were used without further purification.

Normal chromatography was performed with silica gel 60 (Macherey-Nagel, particle size 0.063-0.200 mm) adsorbent, with both isocratic and gradient eluent systems being employed. Thin layer chromatography (TLC) of the compounds was executed on Macherey-Nagel Alugram Sil G/UV254 plates pre-coated with 0.25 mm silica gel 60. The TLC plates were viewed under UV light (254 nm and 366 nm).

Nuclear magnetic resonance (NMR) spectra were recorded on either a Bruker AVANCE 300 MHz or a Bruker AVANCE III 500 MHz spectrometer. All spectra were recorded in chloroform-*d*. All chemical shift values are reported in parts per million referenced against tetramethylsilane which is given an assignment of zero parts per million. Coupling constants (*J*-values) are given in Hertz (Hz).

The infrared spectra were recorded on a Bruker Tensor 27 standard system spectrometer. Measurements were made by loading the sample directly onto a diamond cell. The measurements are reported on the wavenumber scale ($/cm^{-1}$).

Melting points were determined on a Reichert hot-stage microscope, and remain uncorrected. All crystalline compounds were recrystallized from appropriate solvents prior to melting point determination. Microwave reactions were conducted in a CEM Discover microwave.

High resolution mass spectra were obtained with a Waters-LCT-Premier mass spectrometer. The sample was dissolved in methanol to a concentration of 2 ng/µl and introduced by direct infusion. The ionization mode was electrospray positive with a capillary voltage of 2500 V and a desolvation temperature of 250 °C using nitrogen gas at 250 L/hr.

Photochemical reactions were done using a 450W UV power supply source with a Quartz Mercury vapor arc lamp. Reactions were undertaken in a quartz photochemical reactor vessel.

2-Bromo-5-methoxy-1,4-naphthoquinone 10

In a 100 mL round bottom flask equipped with a magnetic stirring bar was placed 2-bromo-5-hydroxy-1,4-naphthoquinone[23] (4.70 g, 18.60 mmol) dissolved in CH_2Cl_2 (60 mL) followed by Ag_2O (10.80 g, 46.63 mmol). To this suspension, MeI (7.92 g, 3.6 mL, 55.81 mmol) was added and the reaction mixture was stirred at r.t. for 24 h under argon. The suspension was filtered through a pad of celite and the solvent removed *in vacuo.* The crude product was purified by column chromatography (silica gel, 30% EtOAc/hexane) to give 2-bromo-5-methoxy-1,4-naphthoquinone **10** as a yellow solid (5.90 g, 17.9 mmol, 96 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (1H, dd, *J* = 7.7, 1.2, H-8), 7.69 (1H, t, *J* = 8.4, H-7), 7.39 (1H, s, H-3), 7.35 (1H, dd, *J* = 8.5, 1.2, H-6), 4.02 (3H, s, OMe); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 181.4, 178.2, 160.0, 142.3, 136.8, 135.0, 133.0, 120.6, 119.3, 118.5, 56.6.[23]

3-Allyl-2-bromo-5-methoxy-1,4-naphthoquinone 12

To a mixture of 2-bromo-5-methoxy-1,4-naphthoquinone **10** (2.20 g, 8.24 mmol) and silver nitrate (0.71 g, 4.18 mmol) in dry MeCN (140 mL) was added vinyl acetic acid (1.42 g, 1.40 mL, 16.48 mmol). The reaction mixture was heated to 65 °C and $(NH_4)_2S_2O_8$ (3. 76 g, 16.48 mmol) in distilled water (120 mL) was added dropwise to the reaction mixture over 30 min. After stirring for 16 h at 65 °C under argon, the cooled reaction mixture was extracted with EtOAc (3 x 100 mL), washed with aq. $NaHCO_3$ (2 x 100 mL) followed by brine (100 mL) and dried over $MgSO_4$. After filtering through celite, the solvent was removed *in vacuo* and the crude product was purified by column chromatography (silica gel, 20-30% EtOAc/hexane) to yield 3-allyl-2-bromo-5-methoxy-1,4-naphthoquinone **12** as a yellow solid (1.82 g, 5.93 mmol, 72%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 (IH, dd, *J* = 7.7, 1.1, H-8), 7.66 (1H, t, *J* = 8.4, H-7), 7.32 (1H, dd, *J* = 8.5, 0.9, H-6), 5.94 – 5.77 (1H, m, =C*H*-), 5.27 (1H, dd, *J* = 17.1, 1.5, =CH_2), 5.12 (1H, dd, *J* = 10.0, 1.4, =CH_2), 4.01 (3H, s, OMe), 3.60 (2H, d, *J* = 6.6, -CH_2-); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 180.2, 178.1, 160.1, 150.6, 136.6, 134.9, 133.3, 131.7, 120.3, 119.2, 118.2, 118.2, 56.6, 35.7. [24]

3-Allyl-2-bromo-1,4,5-trimethoxynaphthalene 8

To a clear solution of 3-allyl-2-bromo-5-methoxy-1,4-naphthoquinone **12** (1.40 g, 4.56 mmol) in THF (80 mL) was added $Na_2S_2O_4$ (3.97 g, 22.80 mmol) in H_2O (25 mL) and TBAI (0.17 g, 0.46 mmol). The reaction was stirred at r.t. under argon for 30 min followed by the addition of KOH (2.56 g, 45.60 mol) in H_2O (140 mL). The reaction was stirred for 1 h and Me_2SO_4 (5.75 g, 4.32 mL, 45.6 mol) was added. The reaction mixture was then stirred for 18 h before being quenched with 25% aq. NH_4OH (100 mL) and the organic material extracted into EtOAc (3 x 100 mL). The combined organic extracts were washed sequentially with distilled water (100 mL), 10% aq. HCl (100 mL) and brine (100 mL). The organic extract was dried over $MgSO_4$, filtered through celite and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10% EtOAc/hexane) to give 3-allyl-2-bromo-1,4,5-trimethoxynaphthalene **8** as a yellowish-brown solid (1.12 g, 3.42 mmol, 75%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 (1H, d, *J* = 8.4, H-8), 7.41 (1H, t, *J* = 8.1, H-7), 6.90 (1H, d, *J* = 7.7, H-6), 6.16 – 5.93 (1H, m, =C*H*-), 5.20 – 4.83 (1H, m, =CH_2), 4.00 (3H, s, OMe), 3.94 (3H, s, OMe), 3.80 (5H, m, OMe and -CH_2-); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.1, 151.2, 149.7, 136.1, 130.4, 129.7, 126.7, 120.0, 117.5, 115.7, 115.0, 106.6, 62.9, 61.1, 56.2, 34.4.[24]

3-Allyl-1,4,5-trimethoxynaphthalen-2-yl-2-boronic acid 7

n-BuLi (1.2 M, 3.02 mL, 3.62 mmol, 2.0 eq.) was added dropwise to a solution of 3-allyl-2-bromo-1,4,5-trimethoxynaphthalene **8** (610 mg, 1.81 mmol, 1.0 eq.) in THF (15 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, then B(O*i*Pr)$_3$ (1.67 mL, 7.24 mmol, 4.0 eq.) was added. The resulting mixture was stirred at −78 °C for a further 30 min and then allowed to warm to r.t. The reaction mixture was made acidic with 10% aq. HCl solution and extracted with Et_2O (3 × 30 mL). The organic layer was then dried with $MgSO_4$ and concentrated under reduced pressure to afford 3-allyl-1,4,5-trimethoxynaphthalen-2-yl-2-boronic acid **7** as an off-white crystalline material (510 mg, 1.70 mmol, 94%), which was used without further purification or characterization.

2-Bromo-5-methoxy-3-methylbenzyl alcohol 16

Method 1: To a stirred solution of 3,5-dimethylanisole **13** (2.07 mL, 14.68 mmol, 1.00 eq.) in CCl_4 (30.0 mL), NBS (2.62 g, 14.68 mmol, 1.00 eq.) and benzoyl peroxide (356 mg, 1.47 mmol) were added at r.t. under argon. The reaction mixture was refluxed for 4 h and after the succinimide was filtered off the filtrate was successively washed with 100 mL each of 10% aq. HCl, sat. aq. $NaHCO_3$, H_2O and brine, before being extracted with CH_2Cl_2 (2 x 100 mL). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used in the next reaction without further purification. To the residue in dioxane (30.0 mL) and H_2O (30.0 mL), was added $CaCO_3$ (2.94 g, 29.36 mmol, 2.00 eq.) at r.t. under argon. The reaction mixture was stirred at reflux for 12 h and then cooled to r.t. and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (100 mL) and dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by chromatography (silica gel, 30% EtOAc/hexane) to afford the benzyl alcohol **16** as an off-white solid (2.37 g, 10.28 mmol, 70%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.86 (1H, d, *J* = 3.2, ArH), 6.69 (1H, d, *J* = 3.1, ArH), 4.64 (2H, s, CH_2OH), 3.75 (3H, s, OMe), 2.85 (1H, br-s, OH), 2.34 (3H, s, ArMe); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.6, 141.0, 139.2, 115.5, 115.1, 111.3, 65.3, 55.4, 23.4. [39]

Method 2: To an ethyl acetate (15 mL) solution of 3,5-dimethylanisole **13** (900 mg, 6.61 mmol, 1.00 eq.), was added benzoyl peroxide (8 mg; 0.033 mmol, 0.5 mol%) and *N*-bromosuccinimide (2.47 g, 13.88 mmol, 2.1 eq.). The reaction mixture was refluxed for 60 min under microwave heating (magnetron power of 300W). The crude product in EtOAc was washed with 30 mL each of 10% HCl, sat. aq. $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and the solvent removed *in vacuo.* The residue was used for the next reaction without further purification. To a stirred solution of the residue in dioxane (30.0 mL) and H_2O (30 mL), $CaCO_3$ (1.32 g, 13.22 mmol, 2.00 eq.) was added at r.t. under argon. The reaction mixture was stirred at reflux for 18 h and then cooled to r.t. and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography (silica gel, 30% EtOAc/hexane) to afford the benzyl alcohol **16** as an off-white solid (1.10 g, 4.76 mmol, 72%).

2-Iodo-3-methoxy-5-methylbenzyl alcohol 17

In an oven-dried 250 mL two-neck round-bottom flask equipped with a magnetic stirring bar was placed **16** (7.62 g, 33.00 mmol) in dry THF (150 mL) under an argon atmosphere. The mixture was cooled to −78 °C and a 1.3 M solution of *n*-BuLi in hexanes (38.08 mL, 49.50 mmol) was added dropwise. The mixture was stirred at −78 °C for 2 h and was then slowly warmed to r.t. The reaction was quenched with water (50 mL) and then extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, 20-30% EtOAc/hexane) to afford the intermediate 3-methoxy-

5-methylbenzyl alcohol as a yellowish oil (4.72 g, 31.02 mmol, 94%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.74 (1H, d, *J* = 0.7, ArH), 6.69 (1H, d, *J* = 0.8, ArH), 6.63 (1H, d, *J* = 0.6, ArH), 4.57 (2H, s, CH_2OH), 3.76 (3H, s, OMe), 2.31 (3H, s, ArMe), 2.28 (1H, brs, OH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.8, 142.4, 139.7, 120.0, 114.0, 109.3, 65.2, 55.2, 21.5. [19] In an oven-dried 50 mL three-neck round-bottom flask equipped with a magnetic stirring bar was placed some of the above 3-methoxy-5-methylbenzyl alcohol (500 mg, 3.29 mmol) in dry Et_2O (17 mL) under argon atmosphere. The mixture was cooled to −78 °C and a 1.2 M solution of *n*-BuLi in hexanes (6.05 mL, 7.26 mmol) was added dropwise. The mixture was then slowly warmed to r.t. and stirred for 4 h. The solution was cooled to 0 °C and THF (9 mL) was then added to the solution and the mixture further stirred for 1 h followed by the slow addition of I_2 (1.00 g, 3.95 mmol)) dissolved in THF (4.0 mL). After being stirred at 0 °C for 30 min, the reaction mixture was poured into aq. $Na_2S_2O_3$ and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by chromatography (silica gel, 20% EtOAc/hexane) to afford 2-iodo-3-methoxy-5-methylbenzyl alcohol **17** as a white crystalline solid (641 mg, 2.31 mmol, 70%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.90 (1H, d, *J* = 0.6, ArH), 6.58 (1H, d, *J* = 0.9, ArH), 4.65 (2H, s, CH_2OH), 3.86 (3H, s, OMe), 2.34 (4H, s, ArMe and OH overlapping); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.8, 144.0, 139.7, 121.8, 111.2, 85.4, 69.6, 56.5, 21.4.[40]

2-Iodo-3-methoxy-5-methylbenzaldehyde 18

In an oven-dried 10 mL round bottom flask equipped with a magnetic stirring bar was placed 2-iodo-3-methoxy-5-methylphenyl)methanol **17** (360 mg, 1.29 mmol) in dry CH_2Cl_2 (5.0 mL). To this solution, MnO_2 (450 mg, 5.2 mmol) was added and the reaction was stirred at r.t. for 24 h. The solution was then filtered through a pad of celite and concentrated *in vacuo.* The crude product was purified by chromatography (silica gel, 20 % EtOAc/hexane) to give 2-iodo-3-methoxy-5-methylbenzaldehyde **18** as an off-white solid (345 mg, 1.25 mmol, 97%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.16 (1H, s, ArCO), 7.31 (1H, s, ArH), 6.88 (1H, s, ArH), 3.93 (3H, s, OMe), 2.39 (3H, s, ArMe); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 196.6, 158.2, 140.0, 136.2, 122.9, 117.2, 90.1, 56.8, 21.1. [27]

2-(2-Allyl-1,4,8-trimethoxynaphthalen-3-yl)-3-methoxy-5-methylbenzaldehyde 19

A deoxygenated solution of 3-allyl-1,4,5-trimethoxynaphthalen-2-yl-2-boronic acid **7** (310 mg, 1.03 mmol, 1.5 eq.) and 2-iodo-3-methoxy-5-methylbenzaldehyde **17** (185 mg, 0.67 mmol, 1.0 eq.) in DME (10 mL) was added to $Pd(PPh_3)_4$ (77 mg, 0.067 mmol, 0.1 eq.) under an argon atmosphere with stirring. To this was added a deoxygenated aq. Na_2CO_3 (2M, 1.34 mL, 2.68 mmol, 4.0 eq.) solution. The mixture was then heated at reflux for 18 h. After this time, the mixture was cooled to r.t. and reaction quenched with H_2O (10 mL). The organic material was extracted into EtOAc (3 x 30 mL), the combined extract dried with $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified by column chromatography (silica gel, 10-20% EtOAc/hexane) to afford 2-(2-allyl-1,4,8-trimethoxynaphthalen-3-yl)-3-methoxy-5-methylbenzaldehyde **19** as an off-white solid (33 mg, 0.08 mmol, 12%). **Mp.** 54-56 °C $CHCl_3$; **FTIR** (v/cm^{-1}): 2944.0 (C-H stretch), 1690.6 (C=O), 1604.1 (C=C), 1568.6, 1446.0, 1054.8 (C-O); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.55 (1H, s, ArCHO), 7.71 (1H, dd, *J* = 8.4, 1.0, H-8´), 7.48 (1H, d, *J* = 0.8, H-6), 7.41 (1H, t, *J* = 8.4, H-7´), 7.04 (1H, d, *J* = 0.9, H-4), 6.93 (1H, dd, *J* = 7.8, 1.0, H-6´), 5.65 (1H, m, =C*H*-), 4.72 (1H, dd, *J* = 10.1, 1.6, =CH_2), 4.50 (1H, dd, *J* = 17.1, 1.8, =CH_2), 4.04 (3H, s, OMe), 3.86 (5H, m, OMe and -CH_2-), 3.74 (3H, s, OMe), 3.45 (3H, s, OMe), 2.49 (3H, s, ArMe). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 192.7, 157.0, 156.1, 150.6, 150.1, 139.3, 136.6, 135.0, 130.1, 129.7, 126.7, 126.0, 125.0, 121.0, 119.2, 116.7, 115.3, 115.1, 106.6, 62.7, 60.7, 56.2, 55.6, 32.1, 21.7; **HRMS** (ESI+): Found $(M + Na)^+$ 429.1657 and $(M + H)^+$ 407.1838, $C_{25}H_{26}O_5$ $(M + Na)^+$ requires 429.1673 and $(M + H)^+$ requires 407.1854, *m/z* 429.1657 [$(M + Na)^+$, 100%], 407.1838 [$(M + H)^+$, 60%].

2-Bromo-1,4,5-trimethoxynaphthalene 22

To a clear solution of 2-bromo-5-methoxy-1,4-naphthoquinone **10**[23] (6.10 g, 22.85 mmol) in THF (380 mL) was added $Na_2S_2O_4$ (19.9 g, 114.30 mmol) in H_2O (100 mL) and TBAI (0.84 g, 2.28 mmol). The reaction was stirred at r.t. under argon for 30 min followed by the addition of KOH (12.8 g, 0.23 mol) in H_2O (300 mL). The reaction was stirred for 1 h and Me_2SO_4 (28.8 g, 21.6 mL, 0.23 mol) was added. The reaction mixture was then stirred for 18 h before being quenched with 25% aq. NH_4OH (150 mL) and the organic material extracted into EtOAc (3 x 200 mL). The combined organic extracts were washed sequentially with distilled water (200 mL), 10% HCl (200 mL) and brine (200 mL). The organic extract was then dried over $MgSO_4$, filtered through celite and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10% EtOAc/hexane) to give 2-bromo-1,4,5-trimethoxynaphthalene **22** as a yellowish-brown solid (5.43 g, 18.1 mmol, 79%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (1H, d, *J* = 8.4, H-8), 7.44 (1H, t, *J* = 8.0, H-7), 6.90 (1H, s, H-3), 6.88 (1H, dd, *J* = 7.8, 0.5, H-6), 3.95 (3H, s, OMe), 3.93 (3H, s, OMe), 3.92 (3H, s, OMe); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.5, 153.9, 146.7, 131.7, 127.5, 117.6 114.6, 112,6, 109.8, 106.9, 61.1, 56.8, 56.4. [23]

(1,4,5-Trimethoxynaphthalen-2-yl)boronic acid 21

n-BuLi (1.5 M, 8.53 mL, 12.80 mmol, 2.0 eq.) was added dropwise to a solution of 2-bromo-1,4,5-trimethoxynaphthalene **22** (1.90 g, 6.40 mmol, 1.0 eq.) in THF (50 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, then $B(OiPr)_3$ (3.61 g, 4.43 mL, 19.20 mmol, 4.0 eq.) was added. The resulting mixture was stirred at −78 °C for a further 30 min and then allowed to warm to r.t. The reaction mixture was acidified with 10% aq. HCl solution and extracted with Et_2O (3 × 50 mL). The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure to afford (1,4,5-trimethoxynaphthalen-2-yl)boronic acid **21** as an off-white crystalline solid (1.61 g, 6.14 mmol, 96%), which was used without further purification or characterization.

3-Methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde 20

A deoxygenated solution of (1,4,5-trimethoxynaphthalen-2-yl)boronic acid **21** (2.50 g, 9.51 mmol, 1.5 eq.) and 2-iodo-3-methoxy-5-methylbenzaldehyde **18** (1.75 g, 6.34 mmol, 1.0 eq.) in DME (80 mL) was added to $Pd(PPh_3)_4$ (10%, 0.73 g, 0.63 mmol) under argon atmosphere with stirring. To this was added a deoxygenated aq. Na_2CO_3 solution (2M 2.69 g, 12.68 mL, 25.36 mmol, 4.0 eq.). The mixture was then heated at reflux for 18 h. After this time, the mixture was cooled to r.t. and reaction quenched with H_2O (100 mL). The organic material was extracted into EtOAc (3 x 100 mL), the combined extracts dried with $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified by column chromatography (silica gel, 10-20% EtOAc/hexane) to afford 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde **20** as an off-white solid (1.85 g, 5.07 mmol, 80%). **Mp.** 160-162 °C CH_2Cl_2; **FTIR** (v/cm^{-1}): 2939 (C-H stretch), 1686.3 (C=O), 1597.6 (C=C), 1118.9 (C-O), 849.6; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.70 (1H, s, ArCHO), 7.75 (1H, dd, *J* = 8.4, 1.0 Hz, H-8′), 7.50 (1H, d, *J* = 0.7 Hz, H-6), 7.44 (1H, t, *J* = 7.9 Hz, H-7′), 7.08 (1H, d, *J* = 0.7 Hz, H-4), 6.93 (1H, dd, *J* = 7.8, 0.7 Hz, H-6′), 6.69 (1H, s, H-3′), 4.00 (3H, s, 5′-OMe), 3.92 (3H, s, 4′-OMe), 3.80 (3H, s, 3-OMe), 3.45 (3H, s, 1′-OMe), 2.49 (3H, s, ArMe); **^{13}C NMR** (126 MHz,

$CDCl_3$) δ 192.8 (ArCHO), 157.4 (C-5′), 157.2 (C-3), 152.8 (C-4′), 147.8 (C-1′), 139.3 (C-5), 134.7 (C-1), 131.2 (C-8′a), 128.1 (C-2′), 126.9 (C-7′), 122.2 (C-2), 119.3 (C-6), 118.6 (C-4′a), 117.2 (C-4), 115.2 (C-8′), 109.7 (C-3′), 107.2 (C-6′), 60.8 (1′-OMe), 56.9 (4′-OMe), 56.6 (5′-OMe), 56.0 (3-OMe), 21.7 (ArMe); **HRMS** (ESI+): Found $[M + H]^+$ 367.1531, $C_{22}H_{23}O_5$ $[M + H]^+$ requires 367.1545, *m/z* 367.1531 (M + H^+, 100%).

2-(2-(2,2-Dibromovinyl)-6-methoxy-4-methylphenyl)-1,4,5-trimethoxynaphthalene 23

In an oven-dried 25 mL round-bottom flask equipped with a magnetic stirring bar was placed PPh_3 (4.98 g, 19.0 mmol, 5.0 eq.) in dry CH_2Cl_2 (6 mL). The mixture was cooled to 0 °C and CBr_4 (3.15 g, 9.50 mmol) was added, and the mixture was stirred for 10 min at 0 °C. Aldehyde **20** (1.40 g, 3.81 mmol, 1.0 eq.) dissolved in dry CH_2Cl_2 (10 mL) was slowly added. The mixture was flushed with argon and allowed to stir at 0 °C for 4 h. The mixture was diluted with CH_2Cl_2 and washed with brine (2 x 30 mL) followed by H_2O (2 x 30 mL). The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layer was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product purified by column chromatography (silica gel, 15-20% EtOAc/hexane) to afford the vinyl dibromide **23** as a foamy yellow solid (1.77 g, 3.40 mmol, 89%). **Mp**. 133-135 °C $(C_2H_5)_2O$; **FTIR** (v/cm^{-1}): 2912 (C-H stretch), 1598.9 (C=C), 1173.2 (C-O); 630.0; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (1H, dd, *J* = 8.4, 1,0, H-8), 7.43 (1H, t, *J* = 8.1, H-7), 7.14 (1H, d, *J* = 0.8, H-3´), 7.09 (1H, s, =C*H*-), 6.91 (1H, dd, *J* = 7.8, 1.1, H-6), 6.84 (1H, d, *J* = 0.9, H-5´), 6.55 (1H, s, H-3), 4.00 (3H, s, OMe), 3.92 (3H, s, OMe), 3.75 (3H, s, OMe), 3.52 (3H, s, OMe), 2.46 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.4, 157.0, 152.8, 147.3, 138.6, 137.1, 136.2, 131.6, 126.5, 124.7, 124.2, 121.7, 118.3, 115.3, 112.1, 109.6, 106.9, 90.6, 61.2, 56.9, 56.6, 55.9, 21.8; **HRMS** (ESI+): Found $[M + H]^+$ 520.9960, $C_{23}H_{23}O_4Br_2$ $[M + H]^+$ requires 520.9963, *m/z* 520.9960 (M + H^+, 50%), 522.9937 (100).

2-(2-Ethynyl-6-methoxy-4-methylphenyl)-1,4,5-trimethoxynaphthalene 24

In an oven-dried 25 mL two-necked round bottom flask equipped with a magnetic stirring bar was placed the vinyl dibromide **23** (1.35 g, 2.59 mmol, 1.0 eq.) in dry THF (6 mL) under argon atmosphere. The mixture was cooled to −78 °C and a 1.2 M solution of *n*-BuLi in hexanes (5.40 mL, 6.48 mmol, 2.5 eq.) was added dropwise. The mixture was allowed to stir at −78 °C for 6 h and then for 1 h at r.t., at which time TLC showed the reaction to be complete. The mixture was quenched with and extracted with Et_2O (3 × 30 mL). The combined organic layer was dried over $MgSO_4$ and solvent evaporated under reduced pressure. Chromatographic purification (silica gel, 20% EtOAc/hexane) afforded the alkyne **24** as a yellowish brown solid (0.83 g, 2.29 mmol, 88 %). **Mp.** 135-137 °C $CHCl_3$; **FTIR** (v/cm^{-1}): 3272.6 (≡C-H stretch), 2946.5 (C-H stretch), 2370.8 (C≡C), 1598.3 (C=C), 1078.3 (C-O); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (1H, dd, *J* = 8.5, 1.0, H-8), 7.41 (1H, t, *J* = 8.2, H-7), 7.09 (1H, d, *J* = 0.9, H-3´), 6.89 (1H, dd, *J* = 8.5, 1,0, H-6), 6.84 (1H, d, *J* = 0.8, H-5´), 6.67 (1H, s, H-3), 3.98 (3H, s, OMe), 3.92 (3H, s, OMe), 3.73 (3H, s, OMe), 3.57 (3H, s, OMe), 2.81 (1H, s, ≡C*H*), 2.41 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.4, 157.1, 152.6, 147.7, 138.6, 131.4, 128.3, 126.2, 125.8, 125.6, 123.2, 118.3, 115.4, 113.0, 109.9, 106.7, 82.6, 79.9, 61.4, 56.9, 56.6, 56.0, 21.5; **HRMS** (ESI+): Found $[M + H]^+$ 363.1601, $C_{23}H_{23}O_4$ $[M + H]^+$ requires 363.1596, *m/z* 363.1601 (M + H^+, 100%), 348.1370 (30).

1,7,8,12-Tetramethoxy-3-methyltetraphene 25 and 1,10,12-trimethoxy-8-methylchrysene 26

Method 1: In an oven-dried 25 mL round bottom flask equipped with a magnetic stirring bar was placed 2-(2-ethynyl-6-methoxy-4-methylphenyl)-1,4,5-trimethoxynaphthalene **24** (810 mg, 2.24 mmol, 1.0 eq.) in dry PhMe (10 mL). $PtCl_2$ (0.089 mg. 0.34 mmol) was then added and the mixture was then stirred at 90 °C for 24 h under an argon atmosphere. The mixture was filtered through celite and the residue was washed with CH_2Cl_2. Chromatographic purification (silica gel, 15-20% EtOAc/hexane) afforded 1,7,8,12-tetramethoxy-3-methyltetraphene **25** as a yellow solid (495 mg, 1.37 mmol, 61 %) and 1,10,12-trimethoxy-8-methylchrysene **26** as yellowish brown solid (171 mg, 0.515 mmol, 23 %). **25: Mp**. 80-82 °C CH_2Cl_2; **FTIR** (v/cm^{-1}): 2919.9 (C-H stretch), 1606.0 (C=C), 1121 (C-O), 1060.3, 832.3**; ^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 (1H, dd, *J* = 8.6, 1.0, H-11), 8.03 (1H, d, *J* = 9.2, H-6), 7.44 (1H, t, *J* = 8.8, H-10), 7.36 (1H, d, *J* = 9.5, H-5), 7.17 (1H, d, *J* = 0.8, H-4), 6.92 (1H, d, *J* = 0.9, H-2), 6.89 (1H, d, *J* = 7.1, H-9), 4.07 (3H, s, 8-OMe), 3.97 (6H, s, 1-OMe and 7-OMe overlapping), 3.51 (3H, s, 12-OMe), 2.54 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.0 (C1-OMe), 156.2 (C8-OMe), 150.9 (C12-OMe), 147.1 (C7-OMe), 138.1 (C-3), 134.6 (C-4a), 129.7 (C-8a), 126.2 (C-5), 125.4 (C-10), 125.1 (C-6a), 122.1 (C-6), 119.6 (C-4), 118.6 (C-7a), 117.4 (C-12a), 116.6 (C-12b), 115.8 (C-11), 110.9 (C-2), 105.2 (C-9), 63.3 (1-OMe), 60.4 (12-OMe), 56.3 (8-OMe), 56.2 (7-OMe), 21.7 (ArMe); **HRMS** (ESI+): Found $[M + H]^+$ 363.1593, $C_{23}H_{23}O_4$ $[M + H]^+$ requires 363.1596, *m/z* 363.1593 (M + H^+, 100%), 362.1521 (55). **26: Mp** 176-178 °C CH_2Cl_2; **FTIR** (v/cm^{-1}): 2904.3 (C-H stretch), 1588.5 (C=C), 1077.4 (C-O); 742.3; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.20 (1H, s, H-11), 8.55 (1H, d, *J* = 9.1, H-5), 8.37 (1H, d, *J* = 8.5, H-4), 7.69 (1H, d, *J* = 9.1, H-6), 7.56 (1H, t, *J* = 8.2, H-3), 7.34 (1H, d, *J* = 0.9, H-7), 7.05 (1H, d, *J* = 7.8, H-2), 6.92 (1H, d, *J* = 0.9, H-9), 4.15 (3H, s, 12-OMe), 4.11 (3H, s, 10-OMe), 4.03 (3H, s, 1-OMe), 2.54 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.6 (C-10), 157.4 (C-1), 154.9 (C-12), 136.5 (C-8), 135.3 (C-6a), 134.0 (C-4a), 130.0 (C-10b), 126.6 (C-3), 124.8 (C-6), 123.5 (C-4b), 122.4 (C-5), 121.2 (C-7), 118.9 (C-10a), 116.7 (C-12a), 116.2 (C-4), 110.0 (C-9), 107.8 (C-2), 106.1 (C-11), 56.8 (1-OMe), 56.2 (10-OMe), 56.1 (12-OMe), 21.7 (ArMe); **HRMS** (ESI+): Found $[M + H]^+$ 333.1387, $C_{22}H_{21}O_3$ $[M + H]^+$ requires 333.1391.

Method 2: In an oven-dried 25 mL round-bottom flask equipped with a magnetic stirring bar was placed 2-(2-ethynyl-6-methoxy-4-methylphenyl)-1,4,5-trimethoxynaphthalene **24** (820 mg, 2.27 mmol, 1.0 eq.) in dry PhMe (10 mL). $AuCl_3$ (0.103 mg. 0.34 mmol) was then added and the mixture was stirred at 90 °C for 24 h under argon atmosphere. The mixture was filtered through celite and the residue was washed with CH_2Cl_2. Chromatographic purification on silica gel (15-20% EtOAc/hexane) afforded 1,7,8,12-tetramethoxy-3-methyltetraphene **25** as a yellow solid (0.460 mg, 1.27 mmol, 56 %) and 1,10,12-trimethoxy-8-methylchrysene **26** as yellowish brown solid (234 mg, 0.704 mmol, 31 %)

1,8-Dimethoxy-3-methyltetraphene-7,12-dione 27

In a 25 mL round bottom flask equipped with a magnetic stirring bar was placed 1,7,8,12-tetramethoxy-3-methyltetraphene **25** (150 mg, 0.41 mmol 1.0 eq.) in MeCN (5 mL). CAN (0.66 mg, 1.20 mmol, 3.0 eq.) in H_2O (5 mL) was then added and the mixture stirred for 30 min. $NaHCO_3$ was then added and organic material was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by column chromatography (silica gel, 50% EtOAc/hexane) to give 1,8,-dimethoxy-3-methyltetraphene-7,12-dione **27** as a yellow solid (117 mg, 0.353 mmol, 86%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.22 (1H, d, *J* = 8.6, H-5), 7.91 (1H, d, *J* = 8.6, H-6), 7.67 (2H, dd, *J* = 4.8, 0.7, ArH), 7.27-7.22 (2H, m, ArH), 6.89 (1H, d, *J* = 1.4, H-2), 4.03 (3H, s, OMe), 3.97 (3H, s, OMe), 2.52 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 186.6, 182.3, 159.4, 156.9, 140.3, 139.3, 137.8, 135.2, 135.0, 133.9, 132.5, 122.7, 120.7, 120.1, 119.1, 118.5, 116.2, 111.2, 56.5, 56.0, 22.1.[11]

Tetrangulol: 1,8-Dihydroxy-3-methyltetraphene-7,12-dione 1

In an oven-dried 25 mL two-necked round bottom flask equipped with a magnetic stirring bar was placed 1,8,-dimethoxy-3-methyltetraphene-7,12-dione **27** (40 mg, 0.120 mmol. 1.0 eq.) in CH_2Cl_2 (5 mL) under argon atmosphere. The mixture was cooled to –78 ˚C and BBr_3 (1.20 mL, 1.20 mmol, 10.0 eq.) was added dropwise. The reaction was then slowly warmed to r.t. and stirred for a further 18 h before being cooled to 0 ˚C and quenched with water. The organic material was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel (5% EtOAc/hexane) to afford a brown solid (34.0 mg) consisting mainly (~85%) of the desired compound, 1,8-dihydroxy-3-methyltetraphene-7,12-dione (tetrangulol) **1** in a similar yield to that published by Hsu.[11] However, **1** co-eluted with small amounts of an unidentified product. (see NMR spectra in supplementary information). The spectroscopic data of the major product **1** agreed with that published previously by Hsu.[11] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 12.24 (1H, s, ArOH), 11.26 (1H, s, ArOH), 8.31 (1H, d, *J* = 8.6, H-5), 8.13 (1H, d, *J* = 8.6, H-6), 7.85 (1H, d, *J* = 7.6, H-11), 7.73 – 7.63 (2H, m, ArH), 7.36 – 7.30 (2H, m, ArH), 7.14 (1H, d, *J* = 1.4, H-2), 2.49 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 189.7, 187.9, 161.7, 155.3, 142.0, 139.1, 137.7, 136.9, 134.8, 132.4, 124.8, 123.2, 121.9, 121.3, 121.2, 120.2, 120.0, 114.7, 21.3.[11]

3-Methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde *O*-acetyl oxime 28a

To a solution of 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde **20** (0.505 g, 1.38 mmol, 1.00 eq.) in MeOH (5 mL) was added hydroxylamine hydrochloride (0.19 g, 2.75 mmol, 2.0 eq.) and NaOAc (0.170 g, 2.07 mmol, 1.5 eq.). The reaction mixture was heated at reflux for 2 h and the solvent was removed *in vacuo.* To the residue, dry CH_2Cl_2 (3 mL) and triethylamine (0.38 mL, 0.28 g, 2.75 mmol, 2.0 eq.) were added at 0 °C. To this cooled solution was slowly added a solution of acetyl chloride (0.2 mL, 0.22 g, 2.75 mmol, 2.0 eq.) in dry CH_2Cl_2 (1 mL). The reaction mixture was stirred at r.t. for 18 h. Upon completion, the reaction was quenched with water (5 mL) and the mixture extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with aq. $NaHCO_3$ (10 mL) and brine (10 mL) and dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel (30 % EtOAc/hexane) to afford the acetyl oxime **28a** as a yellow solid (0.5 g, 1.18 mmol, 86%). **Mp.** 136-138 °C CH_2Cl_2; **FTIR** (v/cm^{-1}): 2946.8 (C-H stretch), 1763.8 (C=O), 1581.1 (C=C), 1449.0, 1374.3 (N-O stretch), 1200.8 (C-O); 751.9; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03 (1H, s, -N=C*H*-), 7.77 (1H, dd, *J* = 8.4, 0.8, H-8´), 7.67 (1H, s, H-6), 7.46 (1H, t, *J* = 8.1, H-7´), 6.97 – 6.92 (2H, m, ArH), 6.57 (1H, s, H-3´), 4.00 (3H, s, OMe), 3.90 (3H, s, OMe), 3.77 (3H, s, OMe), 3.48 (3H, s, OMe), 2.46 (3H, s, ArMe), 2.08 (3H, s, CO_2Me); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6, 157.5, 157.1, 155.3, 155.3, 152.9, 147.4, 139.4, 131.5, 129.6, 126.8, 126.4, 123.5, 119.1, 115.3, 114.7, 109.6, 107.2, 61.0, 56.9, 56.6, 55.9, 21.6, 19.5; **HRMS** (ESI+): Found $[M + H]^+$ 424.1757, $C_{24}H_{26}NO_6$ $[M + H]^+$ requires 424.1760, *m/z* 424.1757 (M + H$^+$, 7%), 364.1542 (100), 333.1357 (30).

3-Methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde *O*-phenyl oxime 28b

O-Phenylhydroxyamine hydrochloride (0.240 g, 1.63 mmol, 1.0 eq.) was dissolved in anhydrous pyridine (10 mL) under argon at r.t. and 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde **20** (0.60 g, 1.63 mmol, 1.0 eq.) was added in one portion. The reaction was stirred at room temperature for 18 hrs. On completion, the reaction was quenched with water and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed three times with $CuSO_4$ to remove traces of pyridine followed by brine and then dried over $MgSO_4$ and the solvent removed *in vacuo.* The crude product was purified by column chromatography (silica gel, 20% EtOAc/hexane) to give the *O*-phenyl oxime **28b** as a yellowish brown solid (0.70 g, 1.53 mmol, 93%). **Mp.** 134-136 °C CH_2Cl_2; **FTIR** (v/cm^{-1}): 2939.5 (C-H stretch), 1578.4 (C=C), 1455.2, 1374.2 (N-O stretch), 1074.6 (C-O); 748.9; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12 (1H, s, -N=C*H*-), 7.78 (1H, dd, *J* = 8.4, 0.9, H-8´), 7.63 (1H, d, *J* = 0.8, H-6), 7.43 (1H, t, *J* = 8.1, H-7´), 7.28 – 7.11 (4H, m, ArH), 7.00 – 6.86 (3H, m, ArH), 6.59 (1H, s, H-3´), 3.97 (3H, s, OMe), 3.89 (3H, s, OMe), 3.74 (3H, s, OMe), 3.52 (3H, s, OMe), 2.47 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.40, 157.47, 157.20, 152.91, 150.84, 147.52, 139.04, 131.51, 130.92, 129.18, 126.76, 125.86, 123.90, 122.05, 118.45, 115.27, 114.41, 113.70, 109.67, 107.11, 60.97, 56.84, 56.58, 55.82, 21.76; **HRMS** (ESI+): Found $[M + H]^+$ 458.1969, $C_{28}H_{28}NO_5$ $[M + H]^+$ requires 458.1967, *m/z* 458.1969 (M + H$^+$, 60%), 364.1548 (100) 334.1434 (30).

3-Methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzonitrile 33

To a solution of the acetyl oxime **28a** (0.32 g, 0.76 mmol, 1.0 eq.) in toluene (10 mL) was added $Pd(dba)_3$ (44 mg, 0.076 mmol, 10 mol%) and Cs_2CO_3 (0.248 g, 0.76 mmol, 1.0 eq.). The reaction was stirred at 150 °C for 24 h. On completion, the reaction mixture was cooled to r.t. followed by the addition of EtOAc (15 mL) and water (15 mL). The organic layer was separated and subsequently washed with a saturated NH_4Cl solution (10 mL), water (10 mL) and brine (10 mL) and dried over $MgSO_4$. The crude product was purified using column chromatography on silica gel (30% EtOAc/hexane) to afford the benzonitrile **33** as a yellow solid (0.17 g, 0.471 mmol, 62%). **Mp.** 184-186 °C $CHCl_3$; **FTIR** (v/cm^{-1}): 2991.3 (C-H stretch), 2364.7 (C≡N), 1597.0 (C=C), 1454.9, 1076.4 (C-O); 846.9.3; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (1H, dd, *J* = 8.4, 1.0, H-8´), 7.43 (1H, t, *J* = 8.2, H-7´), 7.19 (1H, s, H-6), 7.03 (1H, s, H-4), 6.92 (1H, d, *J* = 7.8, H-6´), 6.63 (1H, s, H-3´), 3.98 (3H, s, OMe), 3.93 (3H, s, OMe), 3.77 (3H, s, OMe), 3.55 (3H, s, OMe), 2.44 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.5, 157.3, 153.2, 147.9, 139.9, 131.5, 128.9, 126.8, 125.0, 123.6, 118.9, 118.1, 116.5, 115.4, 114.5, 108.7, 107.4, 61.6, 57.0, 56.7, 56.1, 21.5. **HRMS** (ESI+): Found $[M + H]^+$ 364.1552, $C_{22}H_{22}$ NO_4 $[M + H]^+$ requires 364.1549, *m/z* 364.1552 (M + H$^+$, 100%).

1,10,12-Trimethoxy-8-methylbenzo[*c*]phenanthridine 35

Method 1: O- acetyl oxime **28a** (80 mg, 0.17 mmol, 1.0 eq) was introduced into a UV reactor and *t*-butanol (5 ml) was added and the reaction mixture was degassed with argon. The solution was then subjected to UV radiation (450W) for 20 min. After cooling, the crude product was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford the phenanthridine **35** (26 mg, 0.078 mmol, 46%) and the benzonitrile **33** (11 mg, 0.031 mmol, 18%). **Mp.** 211-213 °C $CHCl_3$); **FTIR** (v/cm^{-1}): 2914.4 (C-H stretch), 1589.4 (C=C), 1446.7, 1363.7, 1075.9 (C-O); 752.2; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.15 (1H, s, H-6), 9.13 (1H, dd, *J* = 8.4, 0.7, H-4), 8.87 (1H, s, H-11), 7.64 (1H, t, *J* = 8.1, H-3), 7.45 (1H, s, H-7), 7.12 (1H, d, *J* = 7.7, H-2), 7.03 (1H, s, H-9), 4.15 (3H, s, 12-OMe), 4.11 (3H, s, 10-OMe), 4.04 (3H, s, 1-OMe), 2.56 (3H, s, ArMe); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.8 (C-10), 156.8 (C-1), 155.4 (C-12), 149.0 (C-6), 137.7 (C-8), 137.2 (C-4b), 135.4 (C-4a), 129.6 (C-6a), 127.0 (C-3), 122.6 (C-10b), 121.0 (C-10a), 120.6 (C-7), 117.9 (C-4), 117.4 (C-12a), 112.7 (C-9), 108.7 (C-2), 103.7 (C-11), 56.8 (1-OMe), 56.1 (10-OMe), 56.0 (12-OMe), 21.8 (ArMe); **HRMS** (ESI+): Found $[M + H]^+$ 334.1447, $C_{21}H_{20}NO_3$ $[M + H]^+$ requires 334.1445, *m/z* 334.1447 (M + H$^+$, 100%), 335.1479 (25), 240.9883 (60).

Method 2: O-phenyl oxime **28b** (110 mg, 0.24 mmol, 1.0eq.) and $EmimPF_6$ (60 mg, 0.24 mmol) were dissolved in *t*-butylbenzene (3 mL) in a microwave reactor tube. The reaction mixture was subjected to microwave irradiation (300W, 160 °C) for 20 min. After cooling, the ionic liquid was filtered off and the crude product was purified by column chromatography (silica gel, 20% EtOAc/hexane) to afford the phenanthridine **35** as a yellow solid (46 mg, 0.14 mmol, 58%) and the benzonitrile **33** (9.60 mg, 0.026 mmol, 11%).

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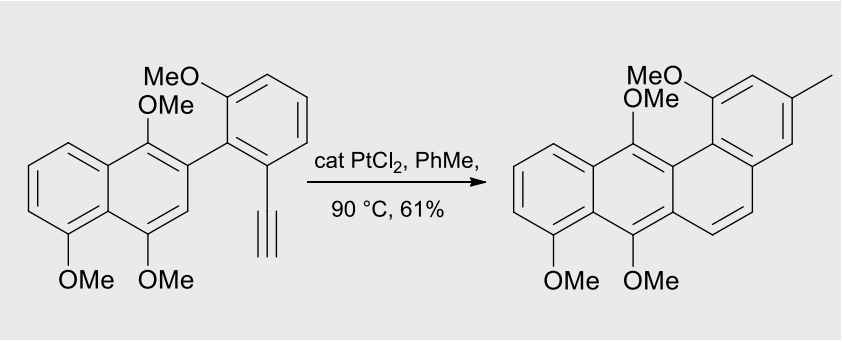

Key Topic*

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Title Reactions of 2-naphthylphenylacetylenes and 2-naphthylbenzaldehyde *O*-phenyl oximes. A synthesis of the angucycline, tetrangulol and 1,10,12

*angucyclines; Suzuki- Miyaura coupling; $PtCl_2$

Cycloisomerization of the biaryl alkyne in the presence of catalytic $PtCl_2$ allowed for the formation of 1,7,8,12-tetramethoxy-3-methyltetraphene, which was easily converted into the natural product tetrangulol.