Directed Metalation–Cross-Coupling Strategies. Total Syntheses of the Alleged and the Revised Phenanthrene Natural Product Gymnopusin

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Dieter Seebach, in Anerkennung seiner Beiträge zur Carbanion-Chemie, Carbanione natürlich, seiner hingebungsvollen und begeisternden Lehrtätigkeit und seiner unaufhörlichen, richtungsweisenden Forschung, gewidmet von einem Chemiker desselben Jahrgangs

The total synthesis of gymnopusin (**2**) is described. The originally assigned structure for gymnopusin **1a** was found to be incorrect by total synthesis using the Directed *ortho*-Metalation (D*o*M)–Cross-Coupling–Directed remote Metalation (DreM) sequence, a demonstrable key strategy for the regioselective construction of the 9-phenanthrol core. The revised structure of gymnopusin (**2**) was confirmed by synthesis by adopting the same strategy but involving a key remote anionic *Fries*-rearrangement step. Both routes highlight methodologies and concepts which may be of value in the regiocontrolled synthesis of phenanthrenoids specifically and in complex polycyclic aromatics in general.

Introduction. – The phenanthrene nucleus is representative of a substantial class of fossil fuel – derived polycyclic aromatic hydrocarbons (PAHs) [1] which is a significant class of soil, sediment, and aquatic environmental pollutants [2]. The phenanthrene PAHs show substantial levels of toxicity towards marine diatoms, gastropods, mussels, crustaceans, and especially fish for which the key biological marker is retene (=7-isopropyl-1-methylphenanthrene) [3], appear as residues in milk, urine, and faeces [4]. Phenanthrenes are also an expanding group of natural products [5], substructures in several major classes of alkaloids [6], common moieties in pharmaceutically and biologically active molecules [7], and, recently, on the wave of interest in material science [8].

In targeting the synthesis of phenanthrenes [9], the strategy adopted for the construction of the core ring has generally involved the initial formation of the C(9)=C(10) bond (stilbene), followed by biaryl ring closure. Following this approach, developed classical methods include *Pschorr* reaction [10], *Mallory* photocyclization[4]), radical cyclization [12], and oxidative coupling [13]. Advances, especially in transition-metal catalytic chemistry, have provided new methods for phenanthrene construction

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[4]) For reviews, see [11a,b]; for recent work, see [11c–i].

[14]. In a contrasting approach, the biaryl bond is formed first, and the core ring is constructed by *i*) the formation of C(9)=C(10) bond through the *McMurry* reaction[5]), and ring-closing metathesis [16]; *ii*) C–C bond-formation between C(9) and C(2) on the side phenyl ring [17]. Other methods for the phenanthrenes-ring construction include benzyne cotrimerization with alkynes[6]) and allenes [19], and biaryl annulation with alkynes [20]. The phenanthrene skeleton can also be constructed by the formation of the side aryl ring, *e.g.*, intramolecular electrophilic cyclization [21], a combined coupling and C(9)=C(10) bond-formation reaction [22], and inter- or intra-molecular cycloaddition [23].

Although an in-depth analysis is required of the above collection of references in order to achieve critical appraisal, most available methodologies suffer, to various degrees, in length, labor, overall yields, and, perhaps most definitively, lack of regiochemical control. As part of recent efforts in carbanionic aromatic chemistry[7]), we are developing routes to a variety of polycondensed aromatics and heteroaromatics which incorporate combined directed *ortho*-metalation (D*o*M), transition metal-catalyzed cross-coupling (mainly *Suzuki–Miyaura* and *Negishi*)[8]), and directed remote metalation (DreM)[9]) reactions. The overall strategy, initially demonstrated for the synthesis of 9-phenanthrols [27], which conceptually inverts the C–C bond-forming steps to those involved in most of the general methods summarized above, constitutes a powerful tool for the regioselective and concise synthesis of polysubstituted aromatics, heteroaromatics, environmental alkylphenanathrenes [27b], and several classes of natural products[10]).

In pursuit of further application of the combined metalation–cross-coupling strategy, we undertook a regioselective synthesis of the phenanthrenoid gymnopusin, the first and only *C(9),C(10)*-dioxygenated phenanthrene natural product from *Bulbophyllum gymnopus* (Orchidaceae) [29] whose structure **1a** (*Scheme 1*) was assigned solely based on its ^{1}H- and ^{13}C-NMR spectra, and those of its diacetate **1b**. In the course of these studies, *Hughes* and *Sargent* [30], and subsequently we [31] demonstrated the incorrectness of the originally assigned structure **1a** and reported on the synthesis of authentic gymnopusin (**2**). At the conclusion of the synthesis of **1a**, we learned of the revised structure **2** [32]. Herein, we report the details of the total synthesis of the natural product **2** and our previously unreported synthesis of the purported gymnopusin structure **1a** and attempts to convert it to the revised gymnopusin structure **2**. Both syntheses take advantage of the versatile D*o*M–cross-coupling synthetic link[8]) but differ in the terminal DreM[9]) approaches.

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5) For reviews, see [15a–c]; for selected work, see [15d,e].

6) For a review, see [18a]; for selected work, see [18b–g].

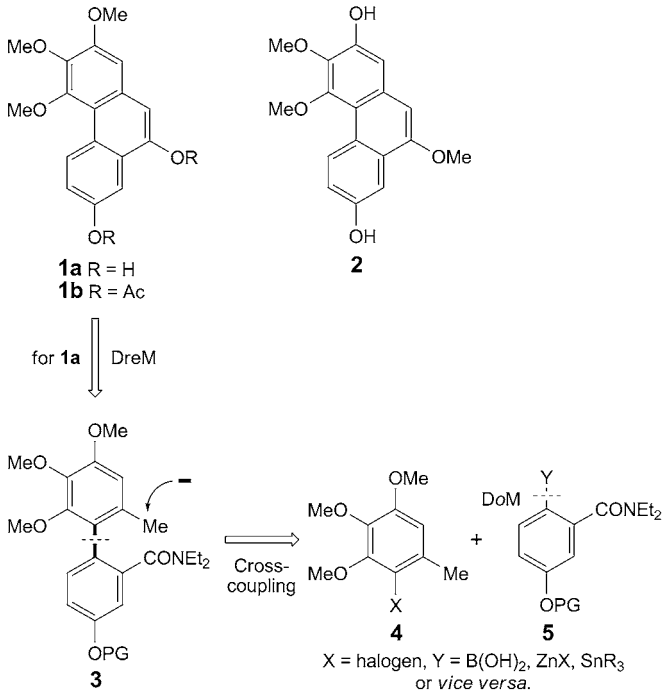
7) For reviews, see [24].

8) For reviews, see [25a,b]; for a historical perspective on the cross-coupling reaction since the 2010 *Nobel* Prize in Chemistry, see [25c].

9) Terminology intended to indicate non-*ortho*-positions. For its conceptual, mechanistic, and synthetic aspects in the context of the complex induced proximity effect (CIPE), see [26].

10) Selected recent examples: azaindoles [28a], benzopyranones [28b], benzocarbazoles and indoloindanones [28c], acridones [28d], indolocarbazoles [28e], liquid-crystal fluorenones [28f].

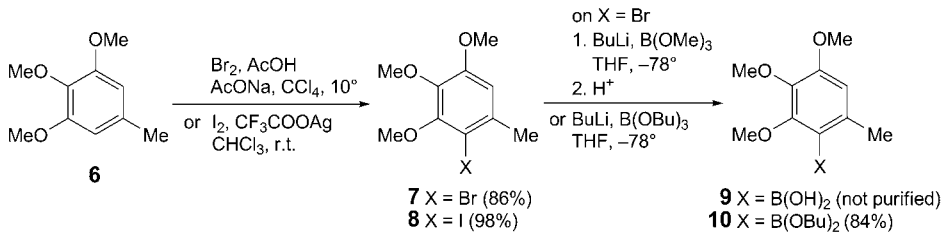
Scheme 1



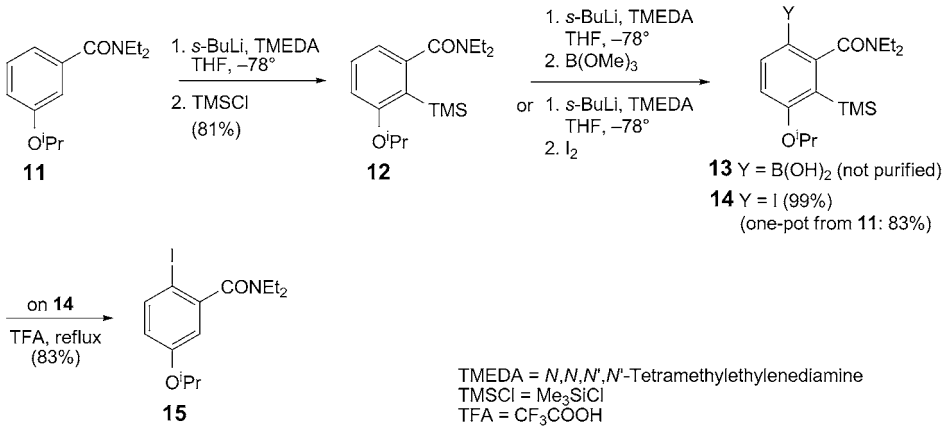
Results and Discussion. – In the retrosynthetic analysis for the originally assigned gymnopusin structure **1a** (*Scheme 1*), C(9)–C(10) bond disconnection conceptualizes the DreM forward step, a vinylogous deprotonation–amide cyclization, from the polyoxygenated biaryl **3**, which, in turn, is envisaged to arise from partners **4** and **5** whose combination (X = metal and Y = halogen) may be inverted giving flexibility to attempt both approaches. Experience gained over some time led to focus on the venerable *Suzuki–Miyaura* protocol ($X = B(OH)_2$, Y = halogen or *vice versa*). Compound **4** is truly readily available, while **5** would originate from D*o*M-controlled regioselective chemistry.

The 2-bromo- and 2-iodo-3,4,5-trimethoxytoluene (**7** and **8**, resp.) were prepared in high yields by adopting classical electrophilic halogenation reactions on commercially available trimethoxytoluene (**6**; *Scheme 2*). The required boronic acid **9** was obtained by a metal/halogen exchange reaction on **7** and quenched with trimethyl borate, followed by acidic workup, and was used without further purification in the cross-coupling reaction (*vide infra*). For reasons which will become apparent, the aqueous stable boronate **10** was also prepared. The requisite boronic acid **13** and iodobenzamide **14** (*Scheme 3*) were prepared by using the silicon protection tactic [33] for the more reactive C–H metalation site in **11**. Thus, metalation–silylation under standard conditions smoothly afforded **12** which upon application of the same metalation conditions, followed by $B(OMe)_3$ and I_2 quenching, furnished the boronic

Scheme 2



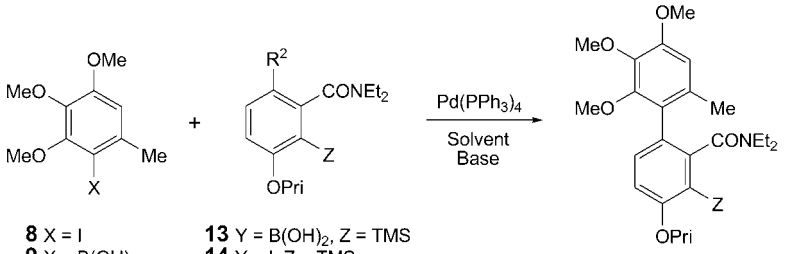
Scheme 3



acid **13** (undetermined yield) and iodo derivative **14** (quant. yield), respectively. An effective one-pot procedure for the conversion of **11** into **14** proceeding in 83% overall yield was also established (see *Exper. Part*). Desilylation of **14** to **15** was achieved by refluxing TFA conditions in high yield [34].

Initial attempts to perform cross-coupling of iodo-toluene **8** with arylboronic acid **13** (*Table*, *Entry 1*) under our standard conditions [35] were unsuccessful leading to recovery of starting **8** (74%) and deboronated benzamide **12** (quant.) which suggested the inhibition of oxidative addition to the Pd catalyst to the sterically congested **8**. To test this tenet, the couplings of the inverted partners, boronic acid **9** and iodo-benzamides **14** and **15**, bearing only one *ortho*-substituent, were carried out (*Entries 2* and *3*). However, these reactions failed to give detectable amounts of the desired biphenyls **16** and **17**, respectively and led to the isolation of product **6**, undoubtedly the result of protodeboronation of **9** under the basic aqueous coupling conditions. In attempts to overcome this problem, the anhydrous conditions described by *Suzuki* and co-workers [36] employing dibutyl borate **10** which was stable to aqueous workup (see *Exper. Part*) and Tl_2CO_3 as the non-aqueous base were adapted. In the event, coupling of **10** with silylated iodo-benzamide **15** using an early *Suzuki* solvent, benzene, gave the first encouraging result – the formation of biaryl **17** in 22% yield (*Entry 4*). Use of the

Table. *Optimization of Conditions for the Synthesis of Biaryls* **16** *and* **17**



8 X = I
9 X = $B(OH)_2$
10 X = $B(OBu)_2$

13 Y = $B(OH)_2$, Z = TMS
14 Y = I, Z = TMS
15 Y = I, Z = H

16 Z = TMS
17 Z = H

Entry	Coupling partners	Conditions	Products (Yield [%])		
1	**8** + **13**	DME, aq. Na_2CO_3, reflux	**16** (0)	**8** (74)	**12** (quant.)
2	**9** + **14**	DME, aq. Na_2CO_3, reflux	**16** (0)	**6** (quant.)	
3	**9** + **15**	DME, aq. Na_2CO_3, reflux	**17** (0)	**6** (quant.)	
4	**10** + **15**	Benzene, Tl_2CO_3, reflux	**17** (22)		
5	**10** + **15**	DME, Tl_2CO_3, reflux	**17** (35)		
6	**10** + **15**	DMF, Tl_2CO_3, 140°	**17** (41)		

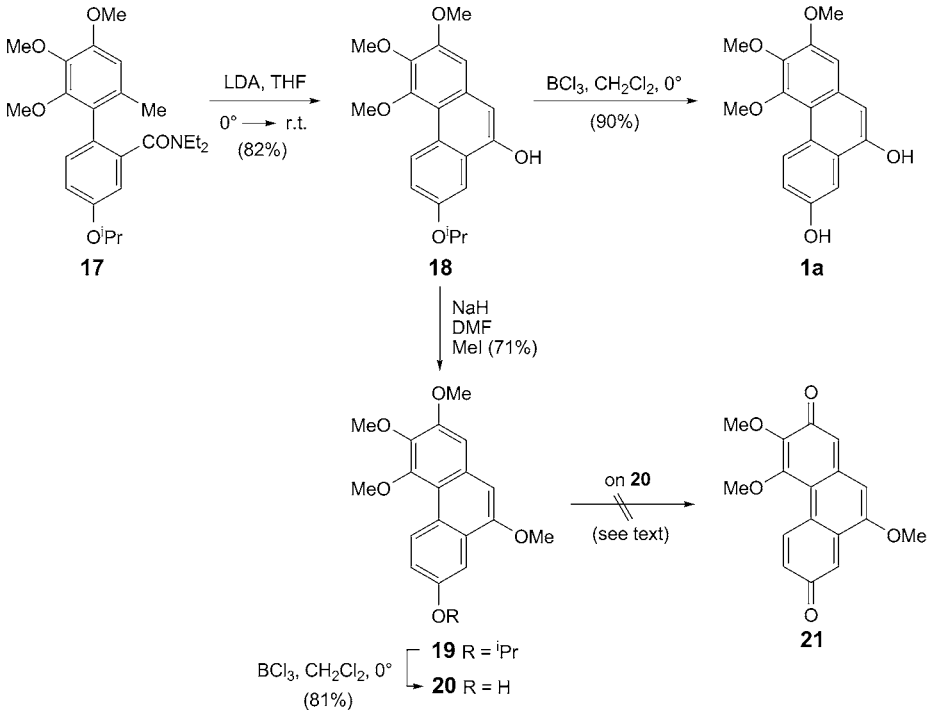
more polar solvents 1,2-dimethoxyethane (DME; *Entry 5*) and DMF (*Entry 6*) showed marked improvement in the formation of **17**, undoubtedly reflecting the increased solubility of the base in these reaction media. The modest optimized yield of 41% of **17** in this cross-coupling reaction is quite remarkable considering the steric factors involved in the mechanistically uncertain *Suzuki–Miyaura* reaction[11]).

With sufficient quantities of **17** in hand, the general LiN^iPr_2 (LDA) protocol used in the 9-phenanthrol synthesis [27c,e] was applied and gave, not without pleasure, the phenanthrol **18** (*Scheme 4*) in 82% yield which, without full characterization, was subjected to selective deisopropylation with BCl_3 [30] to furnish the alleged gymnopusin **1a** in high yield. Dismally, comparison of the melting point and spectroscopic data of **1a** with those reported [29] for the natural product revealed nonidentity (see *Exper. Part*) which were confirmed by *Majumder* and *Banerjee* who proposed [32] a revised structure **2** for gymnopusin.

This setback to our synthetic journey to gymnopusin led to contemplation of potential link compounds between the revised structure **2** and any of the intermediate synthesized phenanthrenes. Thus, inadvertently, compound **18** was still envisaged as a key intermediate which, after a sequence of methylation and deisopropylation, would generate the 7-hydroxyphenanthrene **20**, a compound which may be amenable to oxidation to the extended quinone **21** and hence reduction, steps not without precedent to **2**. In pursuit of translating this suggestion to practice, methylation of **18** under standard conditions smoothly led to **19**, and deprotection with BCl_3 led predictably to **20**. A survey of a plethora of conditions for the oxidation of simple phenols or *para*-methoxyphenols to *para*-benzoquinones (*e.g.*, cerium(IV) ammonium nitrate (CAN)/

[11]) For studies on sterically hindered coupling partners, see [37].

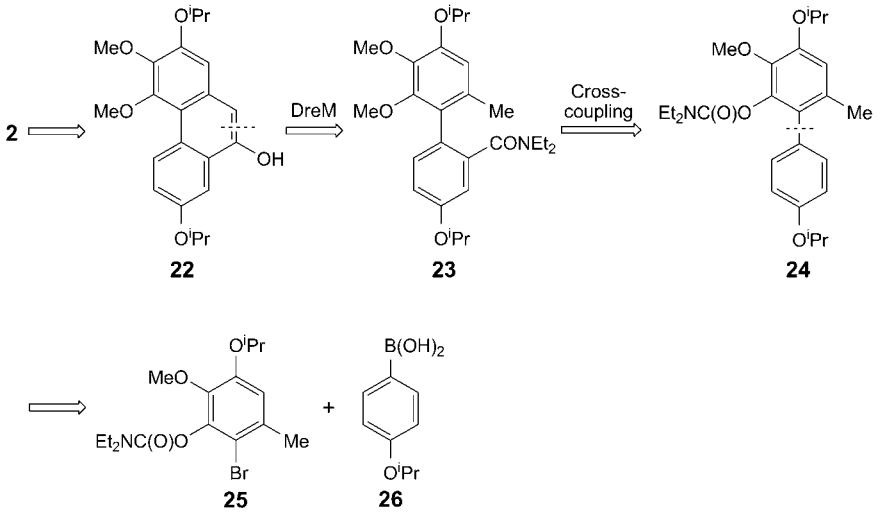
Scheme 4



CH_2Cl_2, CAN/MeCN [38], 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)/MeOH [39], $PhI(O_2CCF_3)_2/K_2CO_3$/MeCN [40], and AgO/MeCN [41]) were unsuccessful and led to complex intractable mixtures of products.

As a new ascent to the revised structure of gymnopusin **2**, and with tenuous assurance of its certainty from the work of *Hughes* and *Sargent* [30], a new retrosynthetic analysis was proposed which takes advantage of the remote anionic *Fries* rearrangement [42]. Thus (*Scheme 5*), a terminal stage methylation and a reasonably assured late stage double deisopropylation [30] leads from target **2** to phenol **22** which, by the DreM disconnection, proceeds to biaryl amide **23**. As the key *retro*-step, remote metalation–carbamoyl ring-to-ring transfer to the symmetrical lower ring of **24** reveals also a perceived benefit of the less sterically hindered *Suzuki–Miyaura* cross-coupling of the bromophenyl carbamate **25** and the readily available boronic acid **26** partners. The challenge is reduced to the preparation of the pentasubstituted benzene **25** bearing five different substituents in which four of the groups have their roles defined: the Br function is required for cross-coupling; the *O*-carbamate, qualitatively the most powerful known directed metalation group (DMG) [43], serves a dual role, first for regioselective Br function introduction by D*o*M, and second, for carbamoyl ring-to-ring transfer, and the ^{i}Pr group is posed to release the phenol by selective deprotection. Only the MeO in starting **25** is maintained throughout the synthesis to the target molecule **2**.

Scheme 5



To initiate the synthesis (*Scheme 6*), commercially available 2,6-dibromo-4-methylphenol was methylated to give **27** whose symmetrical structure allowed mono metal/halogen exchange and boronation–H_2O_2 oxidation to afford **28**. Standard isopropylation to **29**, followed by a second metal/halogen-exchange-mediated OH^+ synthetic-equivalent introduction, smoothly gave **30** which was acylated to afford, in very good overall yield, the carbamate **31** in which the three contiguous O-functionalities are differentiated[12]). Equipped with this powerful *ortho*-metalation director, compound **31** was subjected to regioselective metalation–bromination with $BrCF_2CF_2Br$, a modification of a reported [45] and an improvement of our original procedure [43], to give the bromophenyl carbamate **25**. Cross-coupling of **25** with the aryl boronic acid **26**, straightforwardly prepared from 1-bromo-4-isopropoxybenzene (see *Exper. Part*), under our more customary conditions led to the biaryl **24** in good yield. The key remote ring-to-ring carbamoyl transposition proceeded smoothly using excess LDA in refluxing THF to give compound **32**, which was methylated under standard conditions to furnish the biaryl amide **23**. As anticipated, treatment with BuLi resulted in a vinylogous *ortho*-tolyl metalation–cyclization to give phenanthrol **22**. Due to its somewhat unstable nature, **22** was rapidly methylated to deliver **33** in quantitative yield. Curiously, dimethoxy derivative **33** was also found to be unstable and, therefore, was immediately treated with BCl_3 to afford **2** in excellent yield. Comparison of physical and spectral data of synthetic **2** with those of authentic gymnopusin confirmed identity of the two materials (see *Exper. Part*).

Conclusions. – The syntheses of phenanthrols **1a** (*Scheme 4*) and **2** (*Scheme 6*) have been achieved by application of a combined D*o*M, *Suzuki–Miyaura* cross-coupling,

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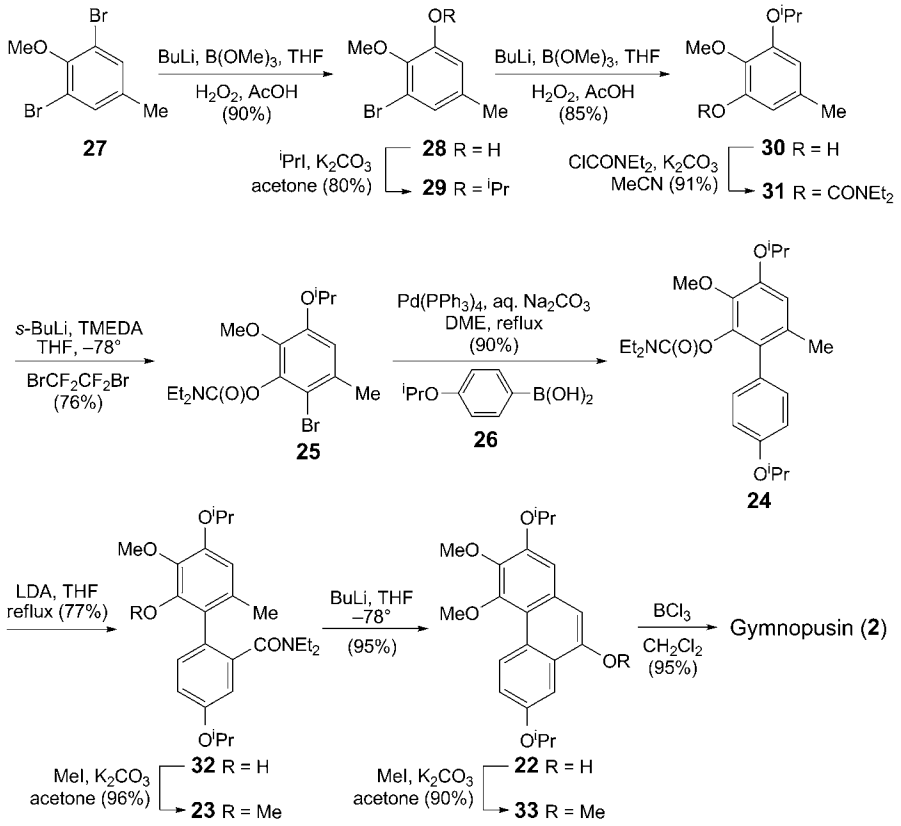
[12]) For other examples of OH^+ equivalent introduction by this tactic, see [44].

Scheme 6



and DreM strategy which differ in a remote anionic *Fries* rearrangement step (*Scheme 6*; **24** → **32**). In the former case, an unnatural (to date) phenanthrenoid was obtained in eight steps and 15% overall yield; in the latter, the natural gymnopusin (**2**) was prepared in twelve steps and 18% overall yield which is comparable to that of *Hughes* and *Sargent* [30] (14 steps, 20% overall yield), all syntheses based on commercially available starting materials. Leaving the discussion of the value of total synthesis for structural confirmation aside, the work may be considered as contributing new features in synthetic methodologies as follows: *a*) provision of conditions of value in highly hindered *Suzuki–Miyaura* couplings (*Table 1*); *b*) the use of the DreM-induced carbamoyl transfer (remote anionic *Fries* rearrangement) as a piggy back method to prepare hindered biaryls that may be difficult or impossible to achieve by direct coupling; *c*) the value of exploring alternate partner coupling-reaction (*i.e.*, **8**, **13** → **10**, **15**, or *vice versa*) concepts to achieve optimum results; *d*) the advantages D*o*M chemistry (silicon protection; *Scheme 3*; **11** → **15**); and *e*) construction of oxygenated aromatics with differential protection (*Scheme 6*; **25**) which may be of further value in contemporary synthetic aromatic chemistry.

Experimental Part

General. All dry solvents used were purified according to *Perrin et al.* [46]. Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and Et_2O were distilled from sodium-benzophenone ketyl under N_2 immediately prior to use. Solns. of BuLi (hexane), *s*-BuLi (cyclohexane) and *t*-BuLi (pentane) were purchased from *Aldrich Chemical Co.*, stored in resealable containers, and titrated periodically against 2,5-dimethoxybenzyl alcohol. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA) was dried over and distilled from CaH_2 before use. Lithium diisopropylamide (LDA) was always prepared before reactions by stirring a 1:1 mixture of $^iPr_2NH$ and BuLi at 0° for 10 min [47]. All commercial materials were purchased from *Aldrich Chemical Co.* or *Lancaster Synthesis Ltd.* Tetrakis(triphenylphosphine)palladium(0) was prepared as described in [48]. All reactions were carried out under N_2 or Ar, unless otherwise specified. The temp. of −78° designated is approximate as achieved by a dry ice/acetone bath. The phrase 'normal workup' means the addition of a sat. aq. NH_4Cl soln. to the reaction mixture, followed by CH_2Cl_2 extraction, drying over Na_2SO_4, filtration, and evaporation of the filtrate *in vacuo* to afford the crude product.

Flash chromatography (FC): *Merck* silica gel *60* (0.04–0.06 mm) purchased from *BDH Chem. Co. Canada* with AcOEt/hexane as eluent unless otherwise specified. Anal. TLC: *Merck* pre-coated silica gel *60F-254* sheets. M.p.: *Büchi* model *SMP-20* instrument; uncorrected. IR Spectra: *Perkin-Elmer 983* IR spectrophotometer, neat between NaCl plates, in $CHCl_3$ soln., nujol, or KBr plate form; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker AC-200* or *AM-250* spectrometers (at 200 and 250 MHz, resp., for ^1H) in $CDCl_3$; chemical shifts, δ, rel. to Me_4Si as internal standard unless otherwise specified; *J* in Hz. MS: and HR-MS by Dr. *R. Smith*, McMaster University, Hamilton, ON, Canada, using *VG 7070F* or *Varian* spectrometers in EI mode unless otherwise specified; *m/z* (rel.). Elemental analysis: by *Galbraith Laboratories*, Knoxville, Tennessee.

(2,3,4-Trimethoxy-6-methylphenyl)boronic Acid (**9**). Prepared by the reaction of **7** with BuLi, followed by $B(OMe)_3$ quenching and acidic workup.

[2-(Diethylcarbamoyl)-4-isopropoxy-3-(trimethylsilyl)phenyl]boronic Acid (**13**). Prepared by the reaction of **12** with *s*-BuLi, TMEDA, followed by $B(OMe)_3$ quenching and acidic workup.

(4-Isopropoxyphenyl)boronic Acid (**26**). Prepared by the reaction of 1-bromo-4-isopropoxybenzene with BuLi, followed by $B(OMe)_3$ quenching and acidic workup.

All these boronic acids were used in cross-coupling reactions without purification.

2-Bromo-3,4,5-trimethoxy-1-methylbenzene (**7**). To a soln. of *1,2,3-trimethoxy-5-methylbenzene* (**6**; 2.75 g, 15.1 mmol), AcONa (1.24 g, 15.0 mmol), and AcOH (0.86 ml, 0.91 g, 15.0 mmol) in CCl_4 (75 ml) was added Br_2 (0.78 ml, 2.41 g, 15.0 mmol) at 10°. The resulting mixture was stirred at r.t. for 2.5 h, subjected to filtration, and the filtrate was washed with dil. Na_2SO_3 soln. Normal workup, followed by FC (AcOEt/hexane 1:3), afforded two products: an early fraction gave 2,6-dibromo-3,4,5-trimethoxytoluene (0.58 g, 11%). Oil. ^1H-NMR: 2.57 (*s*, 3 H); 3.88 (*s*, 6 H); 3.91 (*s*, 3 H). MS: 340 (M^+, 100), 338 (M^+, 51), 325 (20), 323 (10). HR-MS: 337.9151 (M^+, $C_{10}H_{12}Br_2O_3$; calc. 337.9153). A later fraction afforded **7** (3.37 g, 86%). Oil. ^1H-NMR: 2.37 (*s*, 3 H); 3.84 (*s*, 3 H); 3.86 (*s*, 3 H); 3.89 (*s*, 3 H); 6.60 (*s*, 1 H). MS: 262 (M^+, 100), 260 (M^+, 100), 247 (49), 245 (51), 219 (28), 217 (30), 204 (34), 202 (37). HR-MS: 260.0055 (M^+, $C_{10}H_{13}BrO_3^+$; calc. 260.0048).

2-Iodo-3,4,5-trimethoxy-1-methylbenzene (**8**). To a suspension of **6** (1.58 g, 8.7 mmol) and CF_3COOAg (1.92 g, 8.7 mmol) in $CHCl_3$ (10 ml) was added a soln. of I_2 (2.21 g, 8.7 mmol) in $CHCl_3$ (70 ml). The resulting mixture was stirred at r.t. for 3 h, subjected to filtration, and the filtrate was washed with dil. Na_2SO_3 soln. Normal workup, followed by FC (AcOEt/hexane 1:10), afforded 2.61 g (98%) of **8**. M.p. 52–54° (pentane). ^1H-NMR: 2.42 (*s*, 3 H); 3.84 (*s*, 6 H); 3.87 (*s*, 3 H); 6.66 (*s*, 1 H). Anal. calc. for $C_{10}H_{13}O_3$: C 38.98, H 4.25; found: C 39.16, H 4.26.

N,N-*Diethyl-3-isopropoxy-2-(trimethylsilyl)benzamide* (**12**). To a soln. of TMEDA (4.02 ml, 3.10 g, 26.6 mmol) and *s*-BuLi (20.5 ml, 1.30M soln., 26.6 mmol) in THF (100 ml) was added a soln. of N,N-*diethyl-3-isopropoxybenzamide* (**11**; 5.70 g, 24.2 mmol) in THF (20 ml) at −78°. The mixture was stirred at −78° for 1.5 h, neat TMSCl (12.3 ml, 10.52 g, 96.8 mmol) was added at −78°, and the mixture was warmed to r.t. Normal workup, followed by FC (AcOEt/hexane 1:3), afforded 5.99 g (81%) of **12**: B.p. 136–138°/0.05 Torr. IR (neat): 1622. ^1H-NMR: 0.27 (*s*, 9 H); 1.07 (*t*, *J* = 7.2, 3 H); 1.25 (*t*, *J* = 7.2, 3 H);

1.31 – 1.39 (*m*, 6 H); 3.11 – 3.31 (*m*, 2 H); 3.35 – 3.43 (*m*, 1 H); 3.58 – 3.69 (*m*, 1 H); 4.63 (*sept.*, $J = 6.1$, 1 H); 6.66 – 6.70 (*m*, 1 H); 6.76 (*d*, $J = 8.2$, 1 H); 7.27 (*dd*, $J = 8.2, 8.3$, 1 H). EI-MS: 307 (M^+, 1), 293 (23), 292 (100), 250 (34). CI-MS (NH_3): 309 ($[M+2]^+$, 25), 308 ($[M+1]^+$, 100), 292 (15). HR-CI-MS (CH_4): 308.2039 ($[M+H]^+$, $C_{17}H_{30}NO_2Si^+$; calc. 308.2047).

N,N-*Diethyl-6-iodo-3-isopropoxy-2-(trimethylsilyl)benzamide* (**14**). To a soln. of TMEDA (0.83 ml, 0.64 g, 5.5 mmol) and *s*-BuLi (4.23 ml, 1.3M soln., 5.5 mmol) in THF (45 ml) was added a soln. of **12** (1.54 g, 5.0 mmol) in THF (10 ml) at $-78°$. The mixture was stirred at $-78°$ for 1 h, solid I_2 (5.08 g, 20.0 mmol) was added, and the resulting mixture was stirred at r.t. for 10 h and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (50 ml), and the resulting soln. was washed with dil. Na_2SO_3 soln. Normal workup, followed by FC (AcOEt/petroleum ether 2 : 3), afforded 2.16 g (99%) of **14**. M.p. 101 – 102° (hexane/CH_2Cl_2). IR (KBr): 1620. ^{1}H-NMR: 0.26 (*s*, 9 H); 1.12 (*t*, $J = 7.2$, 3 H); 1.28 – 1.38 (*m*, 9 H); 3.02 – 3.27 (*m*, 3 H); 3.87 – 3.98 (*m*, 1 H); 4.54 – 4.64 (*m*, 1 H); 6.51 (*d*, $J = 8.8$, 1 H); 7.70 (*d*, $J = 8.8$, 1 H). MS: 433 (M^+, 9), 419 (22), 418 (100), 376 (12), 319 (9), 177 (14), 149 (29), 137 (15), 129 (11). Anal. calc. for $C_{17}H_{28}INO_2Si$: C 47.11, H 6.51, N 3.23; found: C 47.36, H 6.56, N 3.21.

One-Pot Procedure. To a soln. of TMEDA (0.6 ml, 0.45 g, 3.9 mmol) and *s*-BuLi (3.02 ml, 1.29M soln., 3.9 mmol) in THF (10 ml) was added a soln. of **11** (0.83 g, 3.5 mmol) in THF (5.0 ml) at $-78°$. The mixture was stirred at $-78°$ for 1.5 h, neat TMSCl (0.50 ml, 0.42 g, 3.9 mmol) was added, and the resulting mixture was stirred at r.t. for 10 h. This soln. was added to a soln. of TMEDA (0.59 ml, 0.453 g, 3.9 mmol), and *s*-BuLi (3.0 ml, 1.29M soln., 3.9 mmol) in THF (20 ml) was added at $-78°$ *via* a double-tipped syringe. After stirring at $-78°$ for 1 h, solid I_2 (3.60 g, 14.2 mmol) was added and, the whole was stirred at r.t. for 10 h and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (50 ml), and the soln. was washed with dil. Na_2SO_3 soln. Normal workup, followed by FC (AcOEt/hexane 1 : 2), afforded 1.36 g (83%) of **14** whose physical and spectral properties were identical to those of **14** obtained by the two-step procedure described above.

N,N-*Diethyl-2-iodo-5-isopropoxybenzamide* (**15**). A soln. of **14** (1.52 g, 3.5 mmol) in CF_3COOH (40 ml) was heated at reflux for 10 h, cooled to r.t., and neutralized with 2M Na_2CO_3 until pH 7. Normal workup, followed by FC (AcOEt/hexane 1 : 3), afforded 1.05 g (83%) of **15**. B.p. 135 – 140°/0.01 Torr. IR (neat): 1632. ^{1}H-NMR (CH_2Cl_2 as internal standard): 1.11 (*t*, $J = 7.1$, 3 H); 1.28 – 1.44 (*m*, 9 H); 3.13 – 3.34 (*m*, 3 H); 3.80 – 4.00 (br., 1 H); 4.52 (*sept.*, $J = 6.1$, 1 H); 6.64 (*dd*, $J = 8.7, 2.9$, 1 H); 6.76 (*d*, $J = 2.9$, 1 H); 7.65 (*d*, $J = 8.7$, 1 H). MS: 361 (M^+, 75), 319 (21), 318 (96), 289 (29), 247 (100), 219 (22), 192 (37). HR-MS: 361.0539 (M^+, $C_{14}H_{20}INO_2^+$; calc. 361.0540).

Dibutyl (2,3,4-Trimethoxy-6-methylphenyl)boronate (**10**). To a soln. of **7** (5.23 g, 20 mmol) in THF (100 ml) was added a soln. of *t*-BuLi (26.67 ml of 1.65M, 44.0 mmol) at $-78°$. After 5 min, $B(OMe)_3$ (21.6 ml, 18.4 g, 80 mmol) was added, and the whole was stirred at r.t. for 4 h, concentrated *in vacuo*, and the residue was taken up in CH_2Cl_2 (200 ml). The resulting soln. was subjected to filtration, and the filtrate was concentrated to dryness *in vacuo*. Short-path distillation afforded 5.65 g (84%) of **10**. B.p. 122 – 128°/0.01 Torr. ^{1}H-NMR: 0.87 – 0.94 (*t*, $J = 7.2$, 6 H); 1.29 – 1.64 (*m*, 8 H); 3.79 – 3.87 (*m*, 13 H); 6.48 (*s*, 1 H). MS: 338 (M^+, 91), 337 (22), 282 (42), 182 (100), 167 (26), 165 (60), 151 (25). HR-MS: 338.2267 (M^+, $C_{18}H_{31}BO_5^+$; calc. 338.2265).

N,N-*Diethyl-4-isopropoxy-2′,3′,4′-trimethoxy-6′-methyl-1,1′-biphenyl-2-carboxamide* (**17**). A mixture of $Pd(PPh_3)_4$ (0.03 g, 0.05 mmol), **15** (0.179 g, 0.5 mmol), **10** (0.186 g, 0.57 mmol), and Tl_2CO_3 (0.27 g, 0.57 mmol) in DMF (5 ml) was heated at 140° for 36 h. The resulting mixture was cooled to r.t. and poured onto crushed ice (*ca.* 20 ml). The aq. soln. was extracted with AcOEt (3 × 20 ml), and the AcOEt layer was dried (Na_2SO_4), subjected to filtration, and the filtrate was concentrated *in vacuo* to dryness. FC (AcOEt/hexane 1 : 3) afforded 0.085 g (41%) of **17**. M.p. 106 – 107° (hexane/CH_2Cl_2). IR (KBr): 1610. ^{1}H-NMR: 0.80 (*t*, $J = 7.1$, 3 H); 1.06 (*t*, $J = 7.1$, 3 H); 1.37 (*d*, $J = 6.0$, 3 H); 1.39 (*d*, $J = 6.1$, 3 H); 2.10 (*s*, 3 H); 2.80 – 3.00 (br., 2 H); 3.30 – 3.90 (br., 2 H); 3.64 (*s*, 3 H); 3.81 (*s*, 3 H); 3.85 (*s*, 3 H); 4.57 (*sept.*, $J = 6.1$, 1 H); 6.54 (*s*, 1 H); 6.84 (*d*, $J = 2.6$, 1 H); 6.92 (*dd*, $J = 8.4, 2.6$, 1 H); 7.08 (*d*, $J = 8.4$, 1 H). MS: 415 (M^+, 71), 372 (20), 343 (51), 342 (64), 312 (24), 301 (30), 300 (84), 286 (24), 271 (23), 270 (37), 248 (100). HR-MS: 415.2355 (M^+, $C_{24}H_{33}NO_5^+$; calc. 415.2360).

7-Isopropoxy-2,3,4-trimethoxyphenanthren-9-ol (**18**). To a soln. of LDA (0.52 mmol) in THF (5 ml) was added a soln. of **17** (0.073 g, 0.17 mmol) in THF (2 ml) at 0°. The mixture was stirred at r.t. for 10 h

and acidified with 1N HCl. Normal workup and FC (AcOEt/hexane 1:1) afforded 0.049 g (82%) of **18**, which was used directly for the following reaction.

5,6,7-Trimethoxyphenanthrene-2,10-diol (**1a**). To a soln. of **18** (0.049 g, 0.14 mmol) in CH_2Cl_2 (10 ml) was added BCl_3 (0.57 ml, 1.0M soln. in CH_2Cl_2, 0.07 g, 0.57 mmol) at 0°, and the mixture was stirred at 0° for 20 min and warmed to r.t. Normal workup, followed by FC (AcOEt/hexane), afforded 0.040 g (93%) of **1a**. M.p. 171–173° (hexane/AcOEt). IR (KBr): 3329. ^{1}H-NMR: 3.98 (*s*, 3 H); 3.996 (*s*, 3 H); 4.002 (*s*, 3 H); 6.89 (*s*, 1 H); 6.90 (*s*, 1 H); 7.22 (*dd*, *J* = 9.3, 2.9, 1 H); 7.64 (*d*, *J* = 2.9, 1 H); 9.42 (*d*, *J* = 9.3, 1 H). MS: 300 (M^+, 100), 285 (50), 242 (39). HR-MS: 300.1004 (M^+, $C_{17}H_{16}O_5^+$; calc. 300.0998). These physical and spectral data were found to be different from those reported for gymnopusin [29][30].

7-Isopropoxy-2,3,4,9-tetramethoxyphenanthrene (**19**). To a soln. of NaH (0.017 g, 50% suspension in oil, 0.01 g, 0.36 mmol, washed with benzene) in DMF (3 ml) was added a soln. of **18** (0.061 g, 0.18 mmol) in DMF (2 ml) at r.t. After 30 min, MeI (0.044 ml, 0.10 g, 0.71 mmol) was added, and the mixture was stirred at r.t. for 10 h and poured onto crushed ice (*ca.* 10 ml). The aq. soln. was extracted with AcOEt (3 × 20 ml), and the AcOEt layer was dried (Na_2SO_4), subjected to filtration, and the filtrate was concentrated *in vacuo* to dryness. Prep. TLC (AcOEt/hexane) afforded 0.045 g (71%) of **19**. Oil. ^{1}H-NMR: 1.42 (*d*, *J* = 6.0, 6 H); 3.99 (*s*, 3 H); 4.00 (*s*, 3 H); 4.05 (*s*, 3 H); 4.71 (*sept.*, *J* = 6.0, 1 H); 6.86 (*s*, 1 H); 6.98 (*s*, 1 H); 7.24 (*dd*, *J* = 9.4, 2.9, 1 H); 7.73 (*d*, *J* = 2.9, 1 H); 9.37 (*d*, *J* = 9.4, 1 H). MS: 357 (23), 356 (M^+, 100), 341 (20), 314 (24), 299 (50), 256 (28), 149 (35). HR-MS: 356.1631 (M^+, $C_{21}H_{24}O_5^+$; calc. 356.1624).

5,6,7,10-Tetramethoxyphenanthren-2-ol (**20**). To a soln. of **19** (0.05 g, 0.13 mmol) in CH_2Cl_2 (10 ml) was added BCl_3 (0.25 ml, 1.0M soln. in CH_2Cl_2, 0.03 g, 0.25 mmol) at 0°, and the mixture was stirred for 20 min at 0° and then treated with sat. aq. NH_4Cl soln. at 0°. Normal workup, followed by prep. TLC (AcOEt/hexane 1:2), afforded 0.032 g (81%) of **20**. M.p. 164–166°. ^{1}H-NMR: 3.99 (*s*, 9 H); 4.03 (*s*, 3 H); 5.24 (*s*, 1 H); 6.86 (*s*, 1 H); 6.98 (*s*, 1 H); 7.20 (*dd*, *J* = 9.2, 2.9, 1 H); 7.69 (*d*, *J* = 2.8, 1 H); 9.38 (*d*, *J* = 9.3, 1 H). MS: 314 (M^+, 100), 300 (25), 299 (61), 256 (38). HR-MS: 314.1157 (M^+, $C_{18}H_{18}O_5^+$; calc. 314.1154).

3-Bromo-2-methoxy-5-methylphenol (**28**). To a soln. of *1,3-dibromo-2-methoxy-5-methylbenzene* (**27**; 0.278 g, 1.0 mmol) in THF (10 ml) at −78° was added a soln. of BuLi (1.1 mmol). After stirring for 15 min at −78°, $B(OMe)_3$ (1.7 ml, 1.50 mmol) was added, and the mixture was allowed to warm to r.t. over 4 h. AcOH (1.0 ml) and H_2O_2 (30% soln., 2.0 ml) were added, and the soln. was stirred at r.t. for 8 h and treated with a sat. aq. $Fe(NH_4)_2(SO_4)_2$ soln. to destroy the excess H_2O_2. Normal workup afforded 0.194 g (90%) of **28**. B.p. 85–89°/1 Torr. IR (neat): 3360, 1478. ^{1}H-NMR: 2.22 (*s*, 3 H); 3.87 (*s*, 3 H); 5.65 (*s*, 1 H, exchangeable with D_2O); 6.75 (*d*, *J* = 2, 1 H); 6.89 (*d*, *J* = 2, 1 H). MS: 218 (M^+, 6), 216 (M^+, 6), 137 (100). HR-MS: 215.9787 (M^+, $C_8H_9BrO_2^+$; calc. 215.9786).

1-Bromo-3-isopropoxy-2-methoxy-5-methylbenzene (**29**). A soln. of **28** (0.216 g, 1.0 mmol), ^{i}PrI (0.253 g, 1.5 mmol), and K_2CO_3 (0.21 g, 1.5 mmol) in acetone (10 ml) was refluxed for 12 h. Normal workup afforded 0.206 g (80%) of **29**. B.p. 80–85°/1 Torr. IR (neat): 1408. ^{1}H-NMR: 1.35 (*d*, *J* = 6, 6 H); 2.37 (*s*, 3 H); 3.84 (*s*, 3 H); 4.55 (*sept.*, *J* = 6, 1 H); 6.69 (*d*, *J* = 2, 1 H); 6.96 (*d*, *J* = 2, 1 H). MS: 260 (M^+, 3), 258 (M^+, 3), 179 (100). HR-MS: 258.0259 (M^+, $C_{11}H_{15}BrO_2^+$; calc. 258.0256).

3-Isopropoxy-2-methoxy-5-methylphenol (**30**). To a soln. of **29** (0.258 g, 1.0 mmol) in THF (10 ml) at −78° was added a soln. of BuLi (1.05 mmol). After stirring the soln. at −78° for 15 min, $B(OMe)_3$ (1.7 ml, 1.5 mmol) was added. The mixture was warmed to r.t. over 4 h, after which AcOH (1.0 ml) and H_2O_2 (30% soln., 2.0 ml) were sequentially added, and the resulting soln. was stirred for 8 h. Excess H_2O_2 was destroyed with a sat. aq. $Fe(NH_4)_2(SO_4)_2$ soln. Normal workup afforded 0.167 g (85%) of **30**. B.p. 120–130°/1 Torr. IR (neat): 3366, 1570. ^{1}H-NMR: 1.34 (*d*, *J* = 6, 6 H); 2.25 (*s*, 3 H); 3.86 (*s*, 3 H); 4.55 (*sept.*, *J* = 6, 1 H); 5.70 (*s*, 1 H, exchangeable with D_2O); 6.30 (*d*, *J* = 1.5, 1 H); 6.42 (*d*, *J* = 1.5, 1 H). MS: 196 (M^+, 10), 181 (100). HR-MS: 196.1200 (M^+, $C_{11}H_{16}O_3^+$; calc. 196.1099).

3-Isopropoxy-2-methoxy-5-methylphenyl N,N-*Diethylcarbamate* (**31**). A soln. of **30** (0.196 g, 1.0 mmol), $ClCONEt_2$ (0.204 g, 1.5 mmol), and K_2CO_3 (0.207 g, 1.5 mmol) in MeCN (10 ml) was refluxed for 12 h. Normal workup afforded 0.268 g (91%) of **31**. Oil. IR (neat): 1720. ^{1}H-NMR: 1.25 (*t*, *J* = 7, 6 H); 1.35 (*d*, *J* = 6, 6 H); 2.38 (*s*, 3 H); 3.41 (*q*, *J* = 7, 4 H); 3.82 (*s*, 3 H); 4.52 (*sept.*, *J* = 6, 1 H); 6.57 (*s*, 2 H). MS: 295 (M^+, 11), 100 (100). HR-MS: 295.1785 (M^+, $C_{16}H_{25}NO_4^+$; calc. 295.1783).

2-Bromo-5-isopropoxy-6-methoxy-3-methylphenyl N,N-*Diethylcarbamate* (**25**). To a soln. of **31** (0.295 g, 1.0 mmol) in THF (10 ml) at −78° was added a soln. of *s*-BuLi (2.2 mmol). The mixture was stirred at −78° for 1 h, after which $BrCF_2CF_2Br$ (3.0 ml, 2.5 mmol) was added, and the soln. was allowed to warm to r.t. over 12 h. Normal workup afforded 0.283 g (76%) of **25**. Oil: IR (neat): 1718. ^{1}H-NMR: 1.30 (*m*, 6 H); 1.35 (*d*, *J* = 6, 6 H); 2.35 (*s*, 3 H); 3.45 (*m*, 4 H); 3.85 (*s*, 3 H); 4.45 (*sept.*, *J* = 6, 1 H); 6.70 (*s*, 1 H). MS: 375 (M^+, 11), 373 (M^+, 10), 100 (100). HR-MS: 373.0895 (M^+, $C_{16}H_{24}BrNO_4^+$; calc. 373.0889).

4,4′-Bis(isopropoxy)-3-methoxy-6-methylbiphenyl-2-yl N,N-*Diethylcarbamate* (**24**). A soln. of **25** (0.37 g, 1.0 mmol), **26** (0.33 g, 1.5 mmol), $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol), and 2M Na_2CO_3 (5 ml) in DME (20 ml) was refluxed for 24 h. Normal workup afforded 0.386 g (90%) of **24**. Oil: IR (neat): 1713. ^{1}H-NMR: 0.95 (*m*, 6 H); 1.35 (*d*, *J* = 6.0, 6 H); 1.38 (*d*, *J* = 6.0, 6 H); 2.05 (*s*, 3 H); 2.20 (*m*, 4 H); 3.85 (*s*, 3 H); 4.55 (*sept.*, *J* = 6.0, 2 H); 6.70 (*s*, 1 H); 6.90 (*d*, *J* = 8.5, 2 H); 7.10 (*d*, *J* = 8.5, 2 H). ^{13}C-NMR ($CDCl_3$): 13.5, 20.4, 22.2, 22.4, 42.0, 60.6, 69.9, 71.5, 114.9, 115.5, 128.9, 129.2, 131.1, 131.6, 141.1, 143.1, 150.2, 154.0, 156.8. MS: 249 (M^+, 3), 100 (100). HR-MS: 429.2521 (M^+, $C_{25}H_{35}NO_5^+$; calc. 429.2515).

N,N-*Diethyl-2′-hydroxy-4,4′-bis(isopropoxy)-3′-methoxy-6′-methyl-1,1′-biphenyl-2-carboxamide* (**32**). To a soln. of LDA (5 mmol) in THF (10 ml) at 0° was added **24** (0.429 g, 1.00 mmol) in THF (10.0 ml), and the mixture was refluxed for 3 h. Normal workup afforded 0.330 g (77%) of **32**. M.p. 167–168° (AcOEt/hexane). IR (nujol): 3370, 1638. ^{1}H-NMR: 0.80 (*m*, 3 H); 1.00 (*t*, *J* = 7.0, 3 H); 1.34 (*d*, *J* = 6.0, 6 H); 1.47 (*d*, *J* = 6.0, 6 H); 2.05 (*s*, 3 H); 2.8–2.9 (*m*, 4 H); 3.87 (*s*, 3 H); 4.57 (*sept.*, *J* = 6, 2 H); 5.70 (*s*, 1 H, exchangeable with D_2O); 6.35 (*s*, 1 H); 6.54 (*dd*, *J* = 2.6, 8.4, 1 H); 6.84 (*s*, 1 H); 7.12 (*d*, *J* = 8.4, 1 H). MS: 429 (M^+, 21), 329 (100). HR-MS: 429.2516 (M^+, $C_{25}H_{35}NO_5^+$; calc. 429.2515).

N,N-*Diethyl-4,4′-bis(isopropoxy)-2′,3′-dimethoxy-6′-methyl-1,1′-biphenyl-2-carboxamide* (**23**). A soln. of **32** (0.22 g, 0.5 mmol), MeI (0.14 g, 1.0 mmol), and K_2CO_3 (0.14 g, 1.0 mmol) in acetone (10 ml) was refluxed for 18 h. Normal workup afforded 0.212 g (96%) of **23**. M.p. 125–126° (AcOEt/hexane). IR (nujol): 1640. ^{1}H-NMR: 0.77 (*t*, *J* = 7.0, 3 H); 1.03 (*t*, *J* = 7.0, 3 H); 1.33 (*d*, *J* = 6.0, 6 H); 1.38 (*d*, *J* = 6.0, 6 H); 2.05 (*s*, 3 H); 2.8–3.9 (*m*, 4 H); 3.64 (*s*, 3 H); 3.80 (*s*, 3 H); 4.57 (*sept.*, *J* = 6.0, 2 H); 6.52 (*s*, 1 H); 6.84 (*d*, *J* = 2.6, 1 H); 8.91 (*dd*, *J* = 2.6, 8.4, 1 H); 7.07 (*d*, *J* = 8.4, 1 H). MS: 443 (M^+, 11), 343 (100). HR-MS: 443.2674 (M^+, $C_{26}H_{37}NO_5^+$; calc. 443.2672).

2,7-Bis(isopropoxy)-3,4-dimethoxyphenanthren-9-ol (**22**). To a soln. of **23** (0.133 g, 0.30 mmol) in THF (10 ml) at −78° was added BuLi (0.70 mmol), and the mixture was stirred at r.t. for 20 min. Normal workup afforded 0.105 g (95%) of **22**. Oil. IR(neat): 3360. ^{1}H-NMR: 1.41 (*d*, *J* = 6.0, 6 H); 1.45 (*d*, *J* = 6.0, 6H); 3.87 (*s*, 3 H); 3.92 (*s*, 3 H); 4.72 (*sept.*, *J* = 6.0, 1 H); 4.79 (*sept.*, *J* = 6.0, 1 H); 6.73 (*s*, 1 H); 6.89 (*s*, 1 H); 7.14 (*dd*, *J* = 2.9, 9.4, 1 H); 7.70 (*d*, *J* = 2.9, 1 H); 9.30 (*d*, *J* = 9.4, 1 H). MS and anal. data were precluded due to instability.

2,7-Bis(isopropoxy)-3,4,9-trimethoxyphenanthrene (**33**). A soln. of **22** (0.074 g, 0.2 mmol), MeI (0.070 g, 0.5 mmol), and K_2CO_3 (0.055 g, 0.4 mmol) in acetone (20 ml) was refluxed for 3 h. Normal workup afforded 0.069 g (90%) of **33**. Oil: IR (neat): 1578, 1455. ^{1}H-NMR: 1.42 (*d*, *J* = 6.0, 6 H); 1.46 (*d*, *J* = 6.0, 6 H); 3.04 (*s*, 3 H); 3.40 (*s*, 3 H); 4.72 (*sept.*, *J* = 6, 1 H); 4.79 (*sept.*, *J* = 6, 1 H); 6.83 (*s*, 1 H); 6.99 (*s*, 1 H); 7.24 (*dd*, *J* = 2.9, 9.4, 1 H); 7.73 (*d*, *J* = 2.9, 1 H); 9.37 (*d*, *J* = 9.4, 1 H). MS and anal. data collection were precluded due to instability.

3,4,9-Trimethoxyphenanthrene-2,7-diol (*Gymnopusin*; **2**). To a soln. of **33** (0.038 g, 0.10 mmol) in CH_2Cl_2 (10 ml) at 0° was added BCl_3 (2.0 ml, 1.0M soln. in CH_2Cl_2, 0.50 mmol). The mixture was stirred for 30 min at r.t., and the reaction was quenched at 0° with a few drops of H_2O. Normal workup afforded 0.029 g (95%) of **2**. M.p. 195–196° (hexane) ([29]: 192°; [30]: 202–204°). IR (nujol): 3360, 1613, 1578. ^{1}H-NMR: 3.94 (*s*, 3 H); 3.95 (*s*, 3 H); 4.02 (*s*, 3 H); 6.94 (*s*, 1 H); 7.06 (*s*, 1 H); 7.19 (*dd*, *J* = 2.8, 9.2, 1 H); 7.67 (*d*, *J* = 2.8, 1 H); 8.15 (*s*, 1 H, exchangeable with D_2O); 8.53 (*s*, 1 H, exchangeable with D_2O); 9.31 (*d*, *J* = 9.2, 1 H). MS: 300 (M^+, 4), 285 (100). Physical and spectral data are in full accord with those reported [29][30].

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