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Palladium-Catalyzed Annulation of 2,2′-Diiodobiphenyls with Alkynes: Synthesis and Applications of Phenanthrenes

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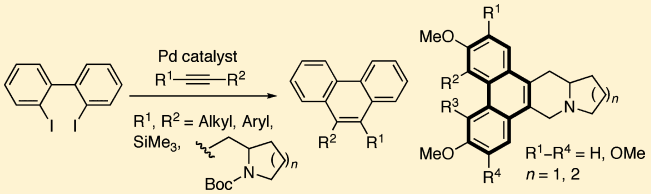
Supporting Information

ABSTRACT: A range of phenanthrene derivatives were efficiently synthesized by the palladium-catalyzed annulation of 2,2′-diiodobiphenyls with alkynes. The scope, limitations and regioselectivity of the reaction were investigated. The described method was adopted to synthesize 9,10-dialkylphenanthrenes, sterically overcrowded 4,5-disubstituted phenanthrenes and phenanthrene-based alkaloids. Reactions of highly methoxy-substituted biphenyls with 2-(2-propynyl)pyrrolidine and 2-(2-propynyl)piperidine gave 2-(9-phenanthylmethyl)pyrrolidines and 2-(9-phenanthylmethyl)piperidines, respectively. The products were transformed to phenanthroindolizidine and phenanthroquinolizidine alkaloids by the Pictet−Spengler reaction.

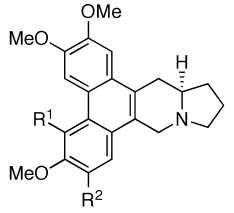


INTRODUCTION

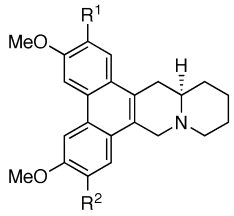
The phenanthroindolizidine and phenanthroquinolizidine alkaloids are formed by the fusion of a highly oxygenated phenanthrene ring to a saturated N-heterocycle,[1] of which tylophorine (**1**), tylocrebrine (**2**), antofine (**3**), cryptopleurine (**4**) and boehmeriasin A (**5**) are representative examples, known for their strong biological properties, including the antitumor, anti-immune and anti-inflammatory properties.[2] With respect to their antitumor properties, many members of these alkaloids are very powerful growth inhibitors ($GI_{50} < 10^{-8}$ M) in the 60 cell-line assay of the National Cancer Institute (NCI) test. (−)-Boehmeriasin A (**5**) is 1−2 orders of magnitude more potent than Paclitaxel (Taxol) in assays for cytotoxicity on a panel of 12 cancer cell lines.[3] However, the cytotoxic potency and the antitumor mechanism of these families of alkaloids are largely unknown,[4] mostly because of their insufficient availability. Many methods for synthesizing these alkaloids have been developed,[5] but a synthetic strategy that involves a *LEGO*-type combination of various building blocks efficiently yields numerous alkaloids. Phenanthrenes are ideal target molecules in the proposed strategy because they can be easily converted to both phenanthroindolizidine and phenanthroquinolizidine alkaloids (Chart 1).

Scheme 1 presents several methods for preparing phenanthrenes. Under irradiation[6] or by transition metal-mediated oxidative coupling,[7] stilbenes are transformed to phenanthrenes (**M1**). Unlike the cyclization of stilbenes, the annulation of biphenyls is widely carried out to synthesize phenanthrenes. In the presence of Lewis acids, for example, 2-ethynylbiphenyl derivatives undergo cyclization to give (iodo)phenanthrenes (**M2**).[8] Additionally, the base-catalyzed cyclization of a 2-(1-propynyl)biphenyl also yields a phenanthrene via an allenyl intermediate.[9] In addition to the aforementioned examples, various metal-catalyzed annulations of biphenyl derivatives with

Chart 1. Representative Examples of Phenanthrene-Based Alkaloids



(−)-(*R*)-**1** (R^1 = H, R^2 = OMe)
(−)-(*R*)-**2** (R^1 = OMe, R^2 = H)
(−)-(*R*)-**3** (R^1 = R^2 = H)



(−)-(*R*)-**4** (R^1 = OMe, R^2 = H)
(−)-(*R*)-**5** (R^1 = H, R^2 = OMe)

alkynes have been reported upon. The biphenyl reactants include 2-iodobiphenyls (**M3**),[10] 2-phenylbenzoic acids (**M3**),[11] 2,2′-diiodobiphenyls (**M4**),[12] and 2-biphenylmagnesium bromide (**M5**).[13] Bis(pinacolatoboryl)alkenes[14] can be regarded as surrogates of alkynes, and they readily undergo palladium-catalyzed Suzuki reactions with 2,2′-dibromobiaryls (**M6**) to yield phenanthrenes.[15] Alternatively, phenanthrenes can be formed by the cycloaddition of an alkyne with a 9-metallafluorene, which is prepared in situ by either the treatment of 2,2′-dilithiobiphenyl with chromium chloride (**M7**)[16] or by the nickel/iridium-catalyzed ring-opening of a biphenylene (**M8**).[17] Moreover, palladium-catalyzed [2+2+2] cycloadditions of arynes with alkynes[18a] or allyl chlorides[18b] also yield phenanthrenes (**M9**). Protocols **M3** and **M4** are the most efficient for preparing various phenanthrene-based alkaloids for the following reasons: (1) most of their reactants or reagents are either commercially available or easily prepared, (2) the desired product can be obtained with few synthetic

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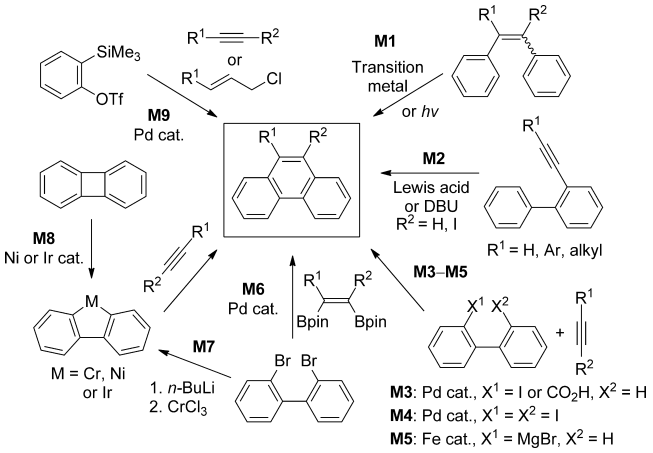
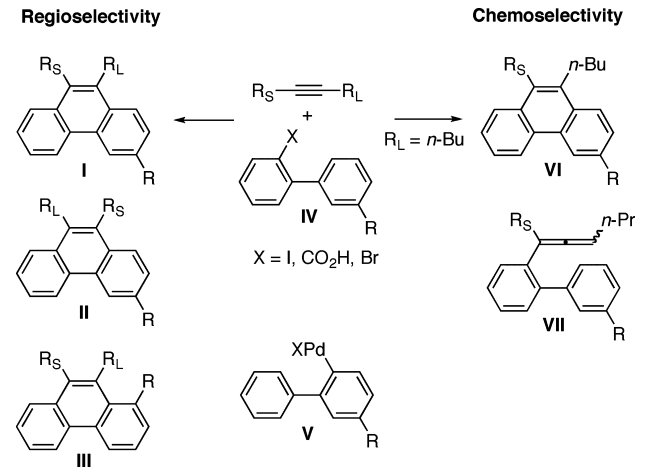
Scheme 1. Preparation of Phenanthrene Derivatives



steps, and (3) as in other palladium-catalyzed protocols, the reaction conditions tolerate many functional groups. In the synthesis of phenanthrene-based alkaloids, reactions must be performed with methoxy-substituted biphenyls.[19]

Efficient synthesis of phenanthrene-based alkaloids depends on the regioselective and chemoselective formation of 9-alkyl- and 9,10-dialkylphenanthrenes. The regioselective formation of phenanthrenes by protocols **M3**–**M8** has been rarely investigated, but it is known to be complicated. For example, the reaction of a biphenyl derivative **IV** with an unsymmetrical alkyne yields up to three regioisomeric products, depending on the reaction conditions (Scheme 2). The expected product is **I**.

Scheme 2. Possible Regioisomers and Byproducts Generated by the Annulation of Biphenyls



One possible byproduct **II** is formed either by reversing the regioselectivity of the alkyne insertion or via a new intermediate **V**, which is furnished by the 1,4-Pd migration of initially generated 2-palladabiphenyl.[20] Another unwanted compound **III** may be yielded in the ring-closure step. The chemoselectivity between **VI** and **VII** is also a serious problem. The byproduct **VII** is formed by β-hydride elimination, which competes with the regular ring-closure step concerning an aryl C–H activation. The protocol **M4** that involves 2,2′-diiodobiphenyls should mitigate the formation of **III** and **VII** because an aryl C–I activation in the ring-closure step should outcompete an aryl C–H activation.

Despite the potential advantages of **M4**, the goals of this investigation include (1) enlarging the scope of the palladium-catalyzed annulation of 2,2′-diiodobiphenyls with an alkyne, (2) reducing the complexity of the regioselectivity, and (3) applying this developed protocol in the synthesis of natural and unnatural phenanthrene-based alkaloids. Notably, the original protocol **M4** cannot be utilized to synthesize phenanthrene-based alkaloids owing to its inefficiency (less than 10% yields for all examples) and narrow scopes.[12]

RESULTS AND DISCUSSION

Heating biphenyl **6a** with 5-decyne (**7a**) under palladium-catalyzed conditions generated a mixture of **8aa** and **9aa** (Table 1). The ligand, silver salts and the reaction temperature strongly affected the reaction efficiency and the **8aa**/**9aa** ratio. AgOAc appeared to outperform Ag_2CO_3 in terms of both reaction efficiency and the selective formation of **8aa**, whose yield was also increased as the reaction temperature was reduced (entries 2, 3, 11, and 13 in Table 1). Ligands IPr, PPh_3, PCy_3, PCy_2Bp, and $P(t\text{-}Bu)_2Bp$ were observed to convert more **6a** than $P(t\text{-}Bu)_3$ did, but they exhibited low chemoselectivity in the formation of **8aa** (entries 4–8 in Table 1). Mixed ligands IPr and $P(t\text{-}Bu)_3$ did not suffer as much from this problem, and gave **8aa** in 76% yield with 98% chemoselectivity (entry 13 in Table 1).

Numerous alkyl-substituted acetylenes **7** under the optimal conditions in this study gave the corresponding phenanthrenes in moderate to good yields with excellent chemoselectivity (Table 2). Only 4-methyl-2-pentyne (**7h**) furnished a significant amount of **9ah** (entry 8 in Table 2). Reactions with sterically congested alkynes **7c** and **7g** or biphenyl **6e** had to be performed at high temperature (entries 3, 7, and 19 in Table 2). Alkyne **7g** formed the desilylated product **8ag′** (entry 7 in Table 2). Unlike *p*-xylene that was used in most of reactions, toluene was a suitable solvent in the reactions of biphenyls **6b** and **6d**, because *p*-xylene underwent side reactions with alkynes to produce dimethylnaphthalene derivatives.[21] These unwanted side reactions were prevented by carefully conducting them in toluene or a mixture of toluene and 1,4-dioxane at low temperature for a longer reaction time (entries 11–14, 17, and 18 in Table 2). Increasing ligand loading also improved the reaction efficiency. This reaction is associated with high chemoselectivity toward aryl iodide, and so the reaction conditions herein can tolerate aryl bromide (entries 17 and 18 in Table 2). Moreover, 2,2′-diiodobiphenyls show unique reactivity in this protocol; their analogues, such as 2-bromobiphenyl or 2,2′-dibromobiphenyl, did not undergo the annulation with 5-decyne (**7a**) to yield 9,10-di-*n*-butylphenanthrene. Dimethyl acetylenedicarboxylate, an electron-deficient alkyne, is not suitable for this reaction because its reaction with biphenyl **6a** generated the corresponding phenanthrene in very low yield (less than 10%).

Unlike the parent phenanthrene,[22] 4,5-disubstituted phenanthrenes exhibit significant out-of-plane distortion,[17a,23] because their bay regions are in an overcrowded environment.[24] Accordingly, both product **8ei** and natural occurring alkaloid (*R*)-**10**, which was isolated from *Tylophora indica*,[25] should have had a twisted phenanthrenyl backbone. On the basis of the number of signals in the ^{13}C NMR spectrum, **8ei** is indeed a twisted molecule. The 2-tolyl substituent would have caused it to contain two conformers (**8ei**-A and **8ei**-B, see Chart 2), which were expected to be observed because a similar compound, 3,4,5,6-tetramethylphenanthrene, has a high

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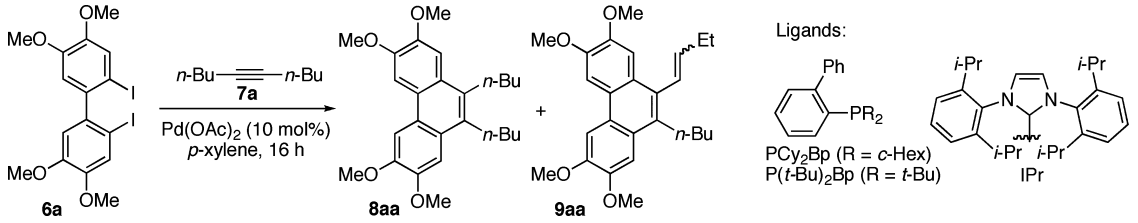
Table 1. Optimization of Reaction Conditions for the Preparation of Phenanthrene 8aa[a]



entry	ligand (mol %)	additive	T (°C)	conversion (%)	**8aa**:**9aa**	yield (%)
1	IPr·HCl (10)	Ag_2CO_3	130	89	69:31	
2	IPr·HCl (10)	Ag_2CO_3	150	85	64:36	
3	IPr·HCl (10)	AgOAc	150	97	74:26	
4	PCy_3 (10)	Ag_2CO_3	150	97	47:53	
5	PPh_3 (10)	Ag_2CO_3	150	57	64:36	
6	PCy_2Bp (10)	Ag_2CO_3	150	69	55:45	
7	P(*t*-Bu)$_2$Bp (10)	Ag_2CO_3	150	92	63:37	
8	P(*t*-Bu)$_3$·HBF_4 (10)	Ag_2CO_3	150	38	96:4	
9	P(*t*-Bu)$_3$·HBF_4 (10)	AgOAc	150	46	98:2	
10	L1/L2 (10/10)	AgOAc	150	86	98:2	
11	L1/L2 (5/5)	AgOAc	150	87	92:8	
12	L1/L2 (5/5)	AgOAc	130	88	97:3	71
13	L1/L2 (5/5)	AgOAc	130	93	98:2	76[b]
14	L1/L2 (3/6)	AgOAc	150	31	100:0	

[a]A reaction mixture comprised with biphenyl **6a** (0.3 mmol), alkyne **7a** (0.6 mmol), $Pd(OAc)_2$ (10 mol %) and Ag_2CO_3 (1.0 equiv), or AgOAc (2.0 equiv) in *p*-xylene was heated if not otherwise mentioned. The ratio of products was determined by GC–MS analysis. Ligand L1 = IPr·HCl, L2 = P(*t*-Bu)$_3$·HBF_4. [b]Reaction for 24 h.

pseudorotation barrier (23.1 kcal/mol) to inverse the configuration.[23a] However, ^{1}H NMR experiments herein could not distinguish the two conformers of **8ei**, even at low temperature (−80 °C).[26]

The regioselectivity of the above protocol was studied using unsymmetrical biphenyl **6g** and alkyne **7b**, and the major product was **8gb**-I (Scheme 3). The structures of **8gb**-I and **8gb**-II were easily determined by conducting NOESY experiments. The electronic effect of biphenyl **6g** and the steric effect of the substituents in alkyne **7b** affected the regioselectivity (Scheme 4).

On the basis of the literature, Scheme 4 describes a putative mechanism for generating phenanthrene **8aa**. Initially, $Pd(OAc)_2$ oxidizes *p*-xylene to produce 2,5-dimethylphenylacetate and 4-methylbenzyl acetate.[27] The oxidative addition reaction of the thus generated Pd(0) species with 2,2′-diiodobiphenyl **6a** gives complex **11**. The *syn*-addition of the Ar–Pd bond in **11** to the triple bond of alkyne **7a** yields the alkenylpalladium derivative **12**. Cyclization of **12** furnishes palladadibenzocycloheptatriene **13**,[28] which forms a mixture of phenanthrene **8aa** and PdI_2 by reductive elimination. The reaction of PdI_2 with added AgOAc eventually reforms $Pd(OAc)_2$. A side reaction of complex **12** produces allene **14** by *β*-hydride elimination, and the latter undergoes palladium-catalyzed cyclization to yield the byproduct **9aa** through *β*-hydride elimination of complex **15**.

The regioselective formation of **8gb**-I in Scheme 3 suggests that the reaction intermediate is not 9-palladafluorene. The mechanism proposed above explains the regioselectivity. The oxidative addition step occurs mainly at the electron-deficient position in **6g** to form complex **16**,[29] which undergoes selective alkyne insertion to yield **17**,[30] and subsequently to **8gb**-I (Scheme 4).

Following the successful examples of the preparation of 9-alkyl- and 9,10-dialkylphenanthrenes, attempts were made to synthesize phenanthroindolizidine and phenanthroquinolizidine alkaloids. As described above, 2-(9-phenanthylmethyl)-pyrrolidines and 2-(9-phenanthylmethyl)piperidines were the key intermediates in this investigation, and they should be obtainable easily by the annulation of biphenyls with corresponding alkynes. On the basis of the authors' recent study, alkyne (*S*)-**7j** was efficiently prepared by the cobalt-catalyzed coupling reaction of (*S*)-2-(iodomethyl)pyrrolidine (*S*)-**18** with trimethylsilylethynylmagnesium (Scheme 5).[5a] This coupling reaction retained the stereochemistry of the pyrrolidinyl backbone. Unfortunately, alkyne (*S*)-**7k** could not be synthesized similarly because iodination of the corresponding alcohol did not yield *N*-Boc-protected (iodomethyl)-piperidine. A modified Corey–Fuchs reaction formed the racemic alkyne **7k** upon the treatment of dibromoalkene **19** with *n*-butyllithium and was followed by the addition of chlorotrimethylsilane.[31]

Alkynes **7j** and **7k** underwent annulation with numerous biphenyls, forming the corresponding phenanthrenes in 45–74% yields in six examples (Table 2). The results strongly depended on the steric properties of both alkynes **7** and biphenyls **6**. Alkyne **7j** produced the cycloadducts in higher yields than **7k** (entries 9, 10, 15, and 16 in Table 2). Relative to other biphenyls, **6e** and **6f** gave unfavorable results (entries 20 and 21 in Table 2) because the former created an overcrowded environment in the bay region of phenanthrenes[23] and the latter resulted in *peri*-repulsion between C-8 and C-9 positions in the phenanthrenyl backbone.[32]

As presented in Schemes 3 and 4, the electronic effect of biphenyl **6g** and the steric effect of alkyne **7b** were assumed to control the regioselective formation of **8gb**-I. Accordingly, the annulation of biphenyl **6h** with alkyne **7k** was expected to exhibit low selectively (Scheme 6), but products **8hk**-I and **8hk**-II are the precursors of cryptopleurine (**4**)[5g] and boehmeriasin

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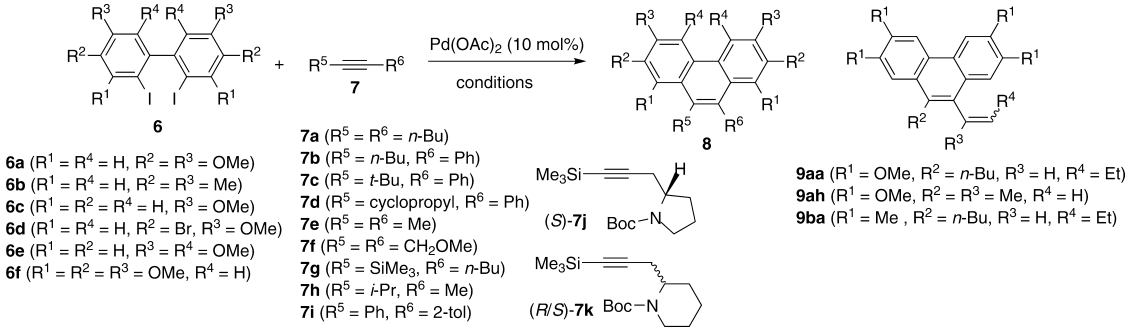
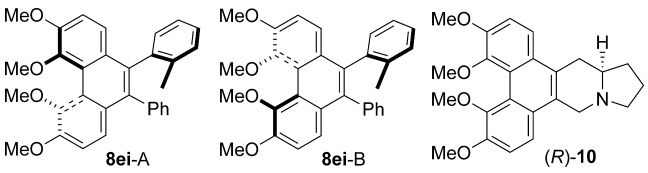
Table 2. Synthesis Phenanthrenes from 2,2′-Diiodobiphenyls 6 and Alkynes 7[a]



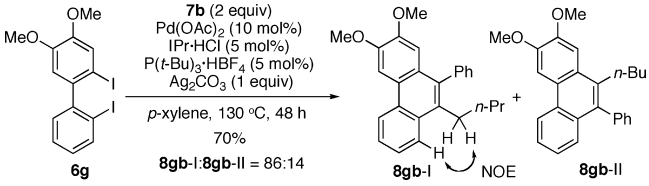
entry	biphenyl	alkyne	ligand (mol %)	salt	solvent	T [°C]/t [h]	product (ratio)	yield (%)
1	**6a**	**7a**	L1/L2 (5/5)	AgOAc	*p*-xylene	130/24	**8aa** + **9aa** (98:2)	76
2	**6a**	**7b**	L1/L2 (5/5)	AgOAc	*p*-xylene	130/24	**8ab**	73
3	**6a**	**7c**	L1 (10)	AgOAc	*p*-xylene	150/24	**8ac**	74
4	**6a**	**7d**	L1/L2 (5/5)	AgOAc	*p*-xylene	130/24	**8ad**	75
5	**6a**	**7e**	L1/L2 (5/5)	AgOAc	*p*-xylene	130/24	**8ae**	63
6	**6a**	**7f**	L1/L2 (5/5)	AgOAc	*p*-xylene	130/24	**8af**	51
7	**6a**	**7g**	L1 (10)	Ag_2CO_3	*p*-xylene	150/24	**8ag′**[b]	68
8	**6a**	**7h**	L1/L2 (5/5)	AgOAc	*p*-xylene	130/24	**8ah** + **9ah** (67:33)	91
9	**6a**	(*S*)-**7j**	L1 (10)	Ag_2CO_3	*p*-xylene	150/16	(*S*)-**8aj**	74[d]
10	**6a**	(*R*/*S*)-**7k**	L1 (10)	Ag_2CO_3	*p*-xylene	150/24	(*R*/*S*)-**8ak**	65
11	**6b**	**7a**	L1/L2 (10/10)	Ag_2CO_3	toluene	90/48	**8ba** + **9ba** (98:2)	67
12	**6b**	**7a**	L1/L2 (10/5)	Ag_2CO_3	toluene[c]	90/48	**8ba** + **9ba** (90:10)	75
13	**6b**	**7b**	L1/L2 (10/10)	Ag_2CO_3	toluene	90/48	**8bb**	70
14	**6b**	**7d**	L1/L2 (10/10)	Ag_2CO_3	toluene	90/48	**8bd**	66
15	**6c**	(*S*)-**7j**	L1 (10)	Ag_2CO_3	*p*-xylene	150/48	(*S*)-**8cj**	65
16	**6c**	(*R*/*S*)-**7k**	L1 (10)	Ag_2CO_3	*p*-xylene	150/48	(*R*/*S*)-**8ck**	51
17	**6d**	**7a**	L1/L2 (10/5)	Ag_2CO_3	toluene[c]	90/72	**8da**	70
18	**6d**	**7b**	L1/L2 (5/5)	Ag_2CO_3	toluene	130/48	**8db**	50
19	**6e**	**7i**	L1/L2 (5/5)	Ag_2CO_3	*p*-xylene	160/48	**8ei**	75
20	**6e**	(*S*)-**7j**	L1 (10)	Ag_2CO_3	*p*-xylene	150/48	(*S*)-**8ej**	50
21	**6f**	(*S*)-**7j**	L1 (10)	Ag_2CO_3	*p*-xylene	150/48	(*S*)-**8fj**	45

[a]The reaction was conducted with biphenyl **6** (0.3 mmol), alkyne **7** (0.6 mmol) and AgOAc (2 equiv) or Ag_2CO_3 (1 equiv). The ratio of products was determined by GC−MS analysis. Ligand L1 = IPr·HCl and L2 = P(*t*-Bu)$_3$·HBF$_4$. [b]A desilylated product **8ag′** (R^5 = H, R^6 = *n*-Bu) was obtained. [c]The reaction was conducted with mixed solvents toluene and dioxane (ratio 4:1). [d]Ref 5a.

Chart 2



Scheme 3. Reaction of Biphenyl 6g with Alkyne 7b



A (**5**), respectively (see below). Indeed, this annulation formed the two regioisomers **8hk**-I and **8hk**-II in approximately equal amounts in a total yield of 64%. Fortunately, they were easily and completely separated from each other.

The Pictet−Spengler reaction converted phenanthrenes **8aj**, **8ej** and **8hk**-II to alkaloids **1**, **10**, and **5**, respectively (Scheme 7). The bioactivity and the synthesis of **10**, unlike those of **1** and **5**, have not yet been elucidated.[33] To the best of the authors' knowledge, a natural phenanthroindolizidine with a highly twisted phenanthrenyl moiety is very rare. Unexpectedly, the analytic data concerning **10** prepared herein differ from these in the literature,[25] but the precise structure of the synthesized product was confirmed by 2D NMR experiments. Consequently, the structure of the alkaloid isolated from *Tylophora indica* must be corrected.[34]

■ CONCLUSION

The synthesis of phenanthrenes by the palladium-catalyzed annulation of 2,2′-diiodobiphenyls with alkynes was investigated. This synthetic method was adopted to prepare important phenanthroindolizidine and phenanthroquinolizidine alkaloids. A significant advantage of this synthetic approach is the *LEGO*-type combination of various biphenyls and pyrrolidinyl or piperidinyl building blocks to give numerous phenanthrene-based alkaloids. Evaluations of their antitumor properties and a systematic study of their structure−activity relationship are currently under way.

■ EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were recorded on 300, 400, and 500 MHz spectrometers. ^{13}C NMR spectra were recorded on 75,

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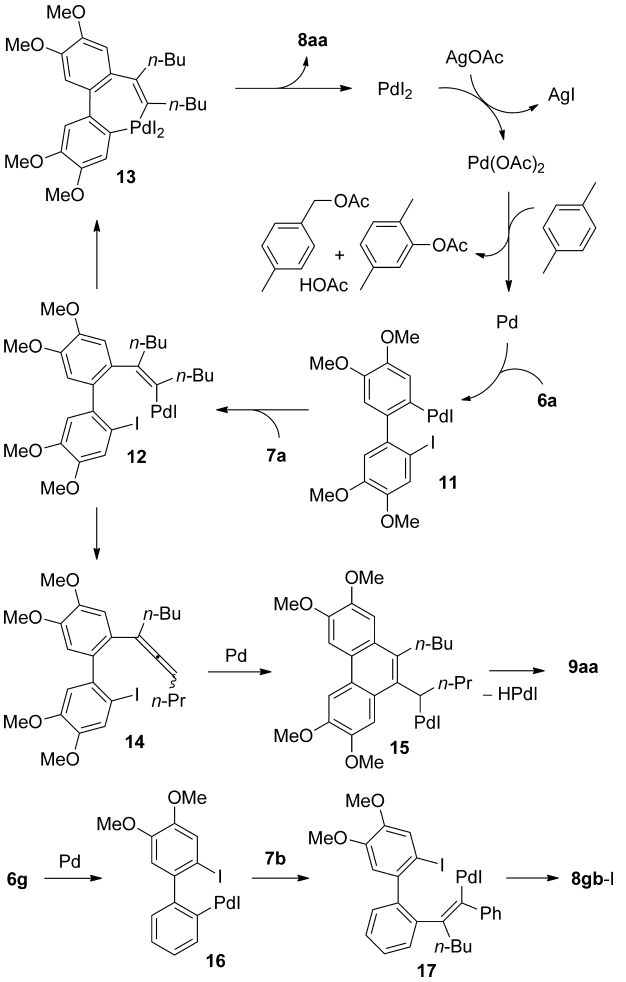
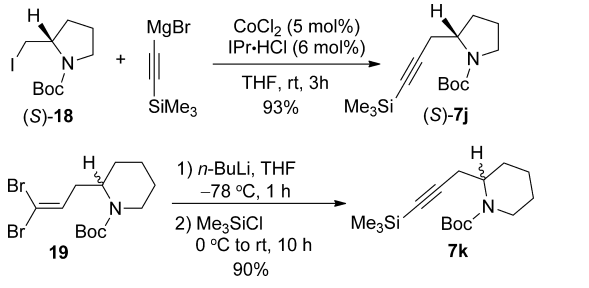
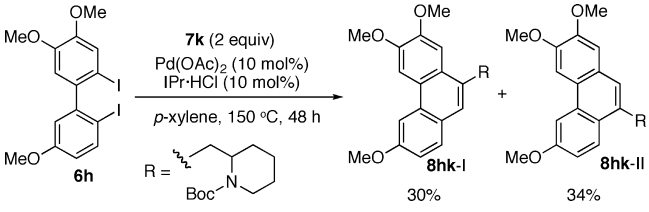
Scheme 4. Proposed Reaction Mechanism for the Formation of 8aa, 8gb-I and 9aa



Scheme 5. Synthesis of Alkynes 7j and 7k



Scheme 6. Reaction of Biphenyl 6h with Alkyne 7k



100, and 125 MHz NMR spectrometers. High-resolution mass spectra (HRMS) were obtained on a high resolution sector type double focusing mass spectrometer (ionization mode: EI or FAB). Melting points were measured by a hot stage melting point apparatus and are uncorrected. Optical rotations were measured at 20 °C from the sodium D line (589 nm) using MeOH or CH_2Cl_2 as solvent. 2,2′-Diiodo-4,4′,5,5′-tetramethoxybiphenyl (**6a**),[35] 2,2′-diiodo-4,4′,5,5′-tetramethylbiphenyl (**6b**),[35] 2,2′-diiodo-4,4′-dibromo-5,5′-dimethoxybiphenyl (**6d**),[36] 1-phenyl-1-hexyne (**7b**),[37] 1-phenyl-3,3-dimethyl-1-butyne (**7c**),[38] 1-cyclopropyl-2-phenylethyne (**7d**),[39] 1,4-dimethoxy-2-butyne (**7f**),[40] 1-trimethylsilyl-1-hexyne (**7g**),[41] 1-methyl-2-(phenylethynyl)benzene (**7i**),[42] and (*S*)-(−)-*tert*-butyl 2-(3-trimethylsilyl-2-propynyl)pyrrolidine-1-carboxylate [(*S*)-**7j**][5a] were synthesized according to or similarly to published procedures. 5-Decyne (**7a**), 2-butyne (**7e**) and 4-methyl-2-pentyne (**7h**) are commercially available.

2,2′-Diiodo-5,5′-dimethoxybiphenyl (6c). The title compound was prepared by the lithium-mediated halogen exchange of 2,2′-dibromo-5,5′-dimethoxybiphenyl. To a solution of 2,2′-dibromo-5,5′-dimethoxybiphenyl[43] (1.86 g, 5.0 mmol) in THF (50 mL) at −78 °C, *n*-butyllithium (4.2 mL, 2.5 M in hexane, 10.5 mmol) was dropwise added. The solution was stirred at the same temperature for 1 h and then treated with a solution of I_2 (2.67 g, 10.5 mmol) in THF (20 mL). The reaction mixture was warmed to room temperature and stirred for 1 h. After adding a saturated aqueous solution of NH_4Cl (30 mL), the aqueous phase was extracted with EA (3 × 20 mL). The combined organic extracts were washed with a saturated aqueous solution of $Na_2S_2O_3$ (50 mL), and dried over $MgSO_4$. The solvents of the filtrate were removed under reduced pressure. The residue was subjected to chromatography on silica gel. Eluting with hexane/EA (10:1) gave **6c** (2.10 g, 90%) as colorless solid: mp 136−137 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 3.80 (s, 6H), 6.69 (dd, J = 8.7, 3.0 Hz, 2H), 6.76 (d, J = 3.0 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 55.5 (OCH_3), 87.8 (C_{quat}), 115.6 (CH), 115.8 (CH), 139.4 (CH), 149.5 (C_{quat}), 159.6 (C_{quat}); EI MS (70 eV), m/z (%) 466 (86) [M^+], 339 (100) [M^+ − I], 212 (27) [M^+ − 2I]; HRMS (EI) calcd for $C_{14}H_{12}I_2O_2$ 465.8927, found 465.8932.

6,6′-Diiodo-2,2′,3,3′-tetramethoxybiphenyl (6e). The title compound was prepared by iodination of 2,2′,3,3′-tetramethoxybiphenyl. A solution of 2,2′,3,3′-tetramethoxybiphenyl[44] (5.48 g, 20.0 mmol) in AcOH (150 mL) was treated with a diluted solution of H_2SO_4 (15 mL, 20% in water), KIO_3 (1.90 g, 8.88 mmol) and I_2 (5.58 g, 22.0 mmol). The reaction mixture was stirred a room temperature for 2 d. A saturated aqueous solution of NH_4Cl (200 mL) was added, and the precipitate was collected and dissolved in ethyl acetate (150 mL). The solution was washed with aqueous $Na_2S_2O_3$ (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate. The solvents of the filtrate were removed under reduced pressure and the residue was subjected to chromatography on silica gel. Eluting with hexane/EA (8:1) gave **6e** (6.00 g, 57%) as colorless solid. Crystallization from ethanol yielded **6e** as colorless crystals: mp 121−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.72 (s, 6H), 3.89 (s, 6H), 6.76 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, plus DEPT, ppm) δ = 55.9 (CH_3), 60.1 (CH_3), 89.5 (C_{quat}), 114.1 (CH), 133.8 (CH), 140.3 (C_{quat}), 147.1 (C_{quat}), 153.2 (C_{quat}); EI MS (70 eV), m/z (%) 526 (100) [M^+], 384 (28) 369 (14); HRMS (EI) calcd for $C_{16}H_{16}I_2O_4$ 525.9138, found 525.9133.

2,2′-Diiodo-3,3′,4,4′,5,5′-hexamethoxybiphenyl (6f). The title compound was prepared by iodination of 3,3′,4,4′,5,5′-hexamethoxybiphenyl. A solution of 3,3′,4,4′,5,5′-hexamethoxybiphenyl[45] (1.00 g, 3.0 mmol) in AcOH (15 mL) was treated with a diluted solution of H_2SO_4 (1.5 mL, 20% in water), KIO_3 (0.28 g, 1.32 mmol) and I_2 (0.84 g 3.30 mmol). The reaction mixture was heated at 80 °C overnight. After cooling to room temperature, water (20 mL) was added. The precipitate was collected and dissolved in ethyl acetate (50 mL). The solution was washed with a saturated aqueous solution of $Na_2S_2O_3$ (30 mL) and brine (30 mL). The organic layer was dried over Mg_2SO_4, and the solvent of filtrate was removed under reduced pressure. The residue was subjected to chromatography on silica gel. Eluting with hexane/EA (3:1) gave **6f** (1.55 g, 88%) as colorless solid: mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.80 (s, 6H), 3.87 (s, 6H), 3.89 (s, 6H), 6.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, plus DEPT, ppm) δ = 56.2 (OCH_3), 60.9 (OCH_3), 61.1 (OCH_3), 87.7 (C_{quat}), 109.6 (CH), 141.4 (C_{quat}), 144.3 (C_{quat}), 153.1 (C_{quat}), 153.4

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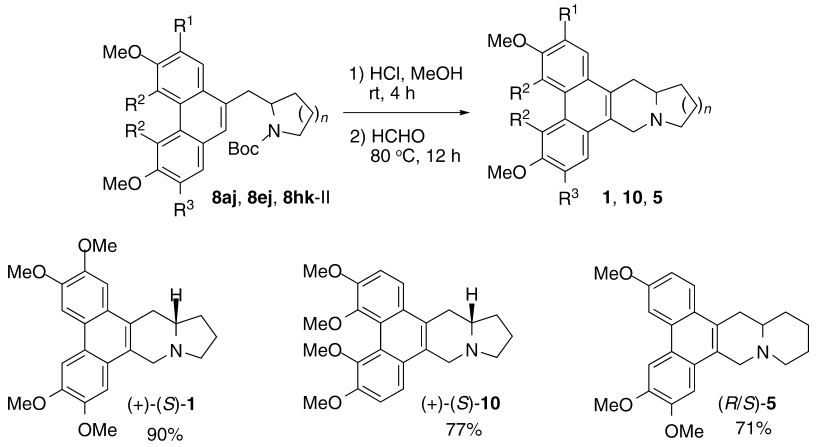
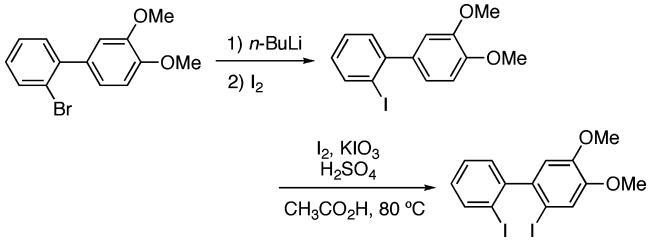
Scheme 7. Synthesis of Alkaloids 1, 5, and 10



(C_{quat}). FAB MS (70 eV), *m*/*z* (%) 586 (15) [M^+], 127 (100); HRMS (FAB) calcd for $C_{18}H_{20}I_2O_6$ 585.9349, found 585.9343.

2,2′-Diiodo-4,5-dimethoxybiphenyl (6g). *(a) Synthesis of 2′-Iodo-3,4-dimethoxybiphenyl.* To a solution of 2′-bromo-3,4-



dimethoxybiphenyl[5b] (2.92 g, 10.0 mmol) in THF (30 mL) at −78 °C, *n*-butyllithium (4.0 mL, 2.5 M in hexane, 10.0 mmol) was dropwise added. The mixture was stirred at the same temperature for 2 h and then treated with a solution of I_2 (2.53 g, 10.0 mmol) in THF (ca. 5 mL). The reaction mixture was warmed to room temperature and stirred for 10 h. A saturated aqueous solution of NH_4Cl (50 mL) was added, and the precipitate was collected and dissolved in ethyl acetate (100 mL). The solution was washed with a saturated aqueous solution of $Na_2S_2O_3$ (30 mL) and brine (30 mL). After drying over $MgSO_4$, the solvents of the filtrate were removed under reduced pressure, and the residue was subjected to chromatography on silica gel. Eluting with hexane/EA (8:1) gave 2′-iodo-3,4-dimethoxybiphenyl (3.06 g, 90%) as colorless solid.

(b) Iodination of 2′-Iodo-3,4-dimethoxybiphenyl. A solution of 2′-iodo-3,4-dimethoxybiphenyl (6.90 g, 20.0 mmol) in AcOH (150 mL) was treated with a diluted solution of H_2SO_4 (15 mL, 20% in water), KIO_3 (0.94 g, 4.40 mmol) and I_2 (2.78 g, 11.0 mmol). The reaction mixture was heated at 80 °C overnight. After cooling to room temperature, water (200 mL) was added. The precipitate was collected and dissolved in ethyl acetate (150 mL), and the solution was washed with a saturated aqueous solution of $Na_2S_2O_3$ (50 mL) and brine (50 mL). After drying over $MgSO_4$, the solvent of the filtrate was removed under reduced pressure, and the residue was subjected to chromatography on silica gel. Eluting with hexane/EA (8:1) gave **6g** (8.38 g, 90%) as colorless solid. Crystallization from ethanol yielded **6g** as colorless crystals: mp 132−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 3.85 (s, 3H), 3.92 (s, 3H), 6.70 (s, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.31 (s, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 56.0 (CH_3), 56.1 (CH_3), 87.5 (C_{quat}), 100.3 (C_{quat}), 112.8 (CH), 120.8 (CH), 127.9 (C_{quat}), 128.8 (CH), 129.3 (CH), 130.3 (CH), 138.9 (CH), 141.6 (C_{quat}), 148.8 (C_{quat}), 149.0 (C_{quat}); EI MS (70 eV), *m*/*z* (%) 466 (100) [M^+], 399 (93), 126 (54); HRMS (EI) calcd for $C_{14}H_{12}I_2O_2$ 465.8927, found 465.8922.

2,2′-Diiodo-4,5,5′-trimethoxybiphenyl (6h). The title compound was prepared by iodination of 2-iodo-3′,4′,5-trimethoxybiphenyl. A solution of 2-iodo-3′,4′,5-trimethoxybiphenyl[5g] (1.11 g, 3.0 mmol) in AcOH (15 mL) at room temperature was treated with a diluted solution of H_2SO_4 (20% in water, 1.5 mL), KIO_3 (0.14 g, 0.67 mmol) and I_2 (0.42 g 1.65 mmol). The reaction mixture was heated at 50 °C for 2 d. After cooling to room temperature, water (20 mL) was added. The precipitate was dissolved in ethyl acetate (50 mL), and the solution was washed with a saturated aqueous solution of $Na_2S_2O_3$ (30 mL) and brine (30 mL). After drying over $MgSO_4$, the solvent of the filtrate was removed under reduced pressure, and the residue was subjected to chromatography on silica gel. Eluting with hexane/EA (5:1) gave **6h** (1.34 g, 90%) as colorless solid: mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.81 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 6.69 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.70 (s, 1H), 6.78 (d, *J* = 2.8 Hz, 1H), 7.31 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, plus DEPT, ppm) δ = 55.5 (OCH_3), 56.0 (OCH_3), 56.2 (OCH_3), 87.3 (C_{quat}), 88.8 (C_{quat}), 112.7 (CH), 115.7 (CH), 116.1 (CH), 120.9 (CH), 139.4 (CH), 141.4 (C_{quat}), 149.0 (2 × C_{quat}), 149.5 (C_{quat}), 159.6 (C_{quat}); EI MS (70 eV), *m*/*z* (%) 496 (100) [M^+], 369 (96) [M^+ − I], 227 (33), 84 (28); HRMS (EI) calcd for $C_{15}H_{14}I_2O_3$ 495.9032, found 495.9031.

***tert*-Butyl 2-(3-trimethylsilyl-2-propynyl)piperidine-1-carboxylate (7k).** To a solution of dibromide **19**[31] (2.39 g, 6.25 mmol) in THF (30 mL) at −78 °C, *n*-butyllithium (5.0 mL, 2.5 M in hexane, 12.5 mmol) was dropwise added. The reaction mixture was kept at the same temperature for 1 h. Then, the solution was warmed to 0 °C and was treated with $SiMe_3Cl$ (1.01 g, 9.37 mmol). After stirring at room temperature overnight, the reaction was quenched with a saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvents of the filtrate were removed under reduced pressure. The residue was subjected to chromatography on silica gel. Eluting with hexane/EA (8:1) gave **7k** (1.66 g, 90%) as pale yellow solid: mp 59−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 0.10 (s, 9H), 1.40 (s, 9H), 1.44−1.60 (m, 5H), 1.80−1.87 (m, 1H), 2.33 (dd, *J* = 16.6, 9.5 Hz, 1H), 2.49 (dd, *J* = 16.6, 5.8 Hz, 1H), 2.67 (t, *J* = 12.7 Hz, 1H), 3.91 (br d, *J* = 12.7 Hz, 1H), 4.31 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, plus DEPT, ppm) δ = 0.0 ($SiMe_3$), 18.6 (CH_2), 20.9 (CH_2), 25.1 (CH_2), 26.6 (CH_2), 28.4 (CH_3), 39.1 (CH_2), 49.6 (CH), 79.3 (C_{quat}), 86.1 and 104.2 (C≡C), 154.7 (C_{quat}); EI MS (70 eV), *m*/*z* (%) 296 (<1) [M^+], 128 (100), 84 (76); HRMS (EI) calcd for $C_{16}H_{29}NO_2Si$ 295.1968, found 295.1969.

Representative Procedure for Preparation of Phenanthrene 8 from 2,2′-Diiodobiphenyl 6 and Alkyne 7. A mixture of the appropriate diiodobiphenyl **6** (0.30 mmol), alkyne **7** (0.60 mmol), $Pd(OAc)_2$ (6.7 mg, 0.30 μmol), IPr·HCl (6.4 mg, 15 μmol), P(*t*-Bu)$_3$·HBF_4 (4.5 mg, 15 μmol), AgOAc (99.0 mg, 0.60 mmol) and *p*-xylene (2 mL) in a thick-walled Pyrex tube was purged with nitrogen for 5 min. The sealed tube was kept in an oil bath at 130 °C for 24 h. After cooling to room temperature, the solvents of the filtrate were

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removed under reduced pressure. The residue was subjected to chromatography on silica gel, eluting with hexane/EtOAc. The analytic data for phenanthrenes (*S*)-**8aj**[5a] and **8hk**-l[5g] have been described previously.

9,10-Di-*n*-butyl-2,3,6,7-tetramethoxyphenanthrene (8aa). Colorless solid: mp 170−171 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 1.07 (t, J = 7.2 Hz, 6H), 1.56−1.71 (m, 8H), 3.10 (t, J = 8.4 Hz, 4H), 4.05 (s, 6H), 4.12 (s, 6H), 7.43 (s, 2H), 7.83 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 14.0 (CH_3), 23.4 (CH_2), 29.2 (CH_2), 32.6 (CH_2), 55.8 (OCH_3), 56.0 (OCH_3), 103.4 (CH), 105.4 (CH), 123.9 (C_{quat}), 125.8 (C_{quat}), 131.5 (C_{quat}), 148.2 (C_{quat}), 148.6 (C_{quat}); EI MS (70 eV), m/z (%) 410 (100) [M^+], 325 (66); HRMS (EI) calcd for $C_{26}H_{34}O_4$ 410.2457, found 410.2446.

9-*n*-Butyl-2,3,6,7-tetramethoxy-10-phenylphenanthrene (8ab). Colorless solid: mp 173−174 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 0.84 (t, J = 7.3 Hz, 3H), 1.25−1.35 (m, 2H), 1.58−1.71 (m, 2H), 2.77−2.82 (m, 2H), 3.70 (s, 3H), 4.06 (s, 3H), 4.11 (s, 3H), 4.15 (s, 3H), 6.65 (s, 1H), 7.30−7.33 (m, 2H), 7.42−7.47 (m, 4H), 7.85 (s, 1H), 7.90 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 13.8 (CH_3), 23.1 (CH_2), 30.3 (CH_2), 32.7 (CH_2), 55.5 (OCH_3), 55.8 (OCH_3), 56.09 (OCH_3), 56.1 (OCH_3), 102.8 (CH), 103.4 (CH), 105.7 (CH), 108.0 (CH), 123.4 (C_{quat}), 124.6 (C_{quat}), 125.3 (C_{quat}), 126.9 (C_{quat}), 127.0 (CH), 128.3 (CH), 130.3 (CH), 132.3 (C_{quat}), 134.8 (C_{quat}), 140.9 (C_{quat}), 148.3 (C_{quat}), 148.5 (C_{quat}), 148.7 (C_{quat}), 148.8 (C_{quat}); EI MS (70 eV), m/z (%) 430 (100) [M^+], 387 (13), 356 (28) HRMS (EI) calcd for $C_{28}H_{30}O_4$ 430.2144, found 430.2141.

9-*tert*-Butyl-2,3,6,7-tetramethoxy-10-phenylphenanthrene (8ac). Colorless solid: mp 142−143 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 1.46 (s, 9H), 3.60 (s, 3H), 4.07 (s, 3H), 4.10 (s, 3H), 4.15 (s, 3H), 6.56 (s, 1H), 7.31−7.42 (m, 5H), 7.79 (s, 1H), 7.87 (s, 1H), 8.00 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 35.1 (CH_3), 38.2 (C_{quat}), 55.3 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 56.1 (OCH_3), 102.3 (CH), 103.3 (CH), 108.6 (CH), 111.0 (CH), 123.6 (C_{quat}), 125.8 (C_{quat}), 126.1 (C_{quat}), 126.9 (CH), 127.4 (CH), 127.9 (C_{quat}), 131.7 (CH), 134.6 (C_{quat}), 138.5 (C_{quat}), 143.5 (C_{quat}), 146.4 (C_{quat}), 147.9 (C_{quat}), 148.0 (C_{quat}), 148.7 (C_{quat}); EI MS (70 eV), m/z (%) 430 (100) [M^+], 415 (22), 369 (12); HRMS (EI) calcd for $C_{28}H_{30}O_4$ 430.2144, found 430.2134.

9-Cyclopropyl-2,3,6,7-tetramethoxy-10-phenylphenanthrene (8ad). Colorless solid: mp 150−151 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 0.30−0.35 (m, 2H), 0.75−0.81 (m, 2H), 1.99−2.08 (m, 1H), 3.72 (s, 3H), 4.08 (s, 3H), 4.12 (s, 3H), 4.15 (s, 3H), 6.98 (s, 1H), 7.37−7.50 (m, 5H), 7.85 (s, 1H), 7.87 (s, 1H), 8.09 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 9.5 (CH_2), 13.3 (CH), 55.5 (OCH_3), 55.8 (OCH_3), 56.08 (OCH_3), 56.09 (OCH_3), 102.7 (CH), 103.0 (CH), 106.9 (CH), 107.7 (CH), 124.0 (C_{quat}), 124.2 (C_{quat}), 126.3 (C_{quat}), 126.7 (CH), 127.5 (C_{quat}), 127.9 (CH), 131.0 (CH), 131.4 (C_{quat}), 136.8 (C_{quat}), 140.7 (C_{quat}), 148.3 (C_{quat}), 148.4 (C_{quat}), 148.7 (C_{quat}), 148.8 (C_{quat}), EI MS (70 eV), m/z (%) 414 (58) [M^+], 383 (100), 352 (18); HRMS (EI) calcd for $C_{27}H_{26}O_4$ 414.1831, found 414.1829.

2,3,6,7-Tetramethoxy-9,10-dimethylphenanthrene (8ae). Colorless solid: mp 210−211 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 2.68 (s, 6H), 4.06 (s, 6H), 4.12 (s, 6H), 7.40 (s, 2H), 7.83 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 16.2 (CH_3), 55.8 (OCH_3), 56.0 (OCH_3), 103.3 (CH), 105.3 (CH), 123.4 (C_{quat}), 126.6 (C_{quat}), 126.9 (C_{quat}), 148.2 (C_{quat}), 148.6 (C_{quat}); EI MS (70 eV), m/z (%) 326 (100) [M^+], 268 (16); HRMS (EI) calcd for $C_{20}H_{22}O_4$ 326.1518, found 326.1517.

2,3,6,7-Tetramethoxy-9,10-bis(methoxymethyl)-phenanthrene (8af). Colorless solid: mp 187−188 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 3.52 (s, 6H), 4.06 (s, 6H), 4.11 (s, 6H), 5.03 (s, 4H), 7.59 (s, 2H), 7.80 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 55.8 (OCH_3), 56.0 (OCH_3), 58.1 (OCH_3), 68.4 (CH_2), 102.9 (CH), 106.0 (CH), 125.3 (C_{quat}), 125.6 (C_{quat}), 129.2 (C_{quat}), 148.8 (C_{quat}), 149.3 (C_{quat}); EI MS (70 eV) m/z (%) 386 (100) [M^+], 354 (43), 339 (64); HRMS (EI) calcd for $C_{22}H_{26}O_6$ 386.1729, found 386.1720.

9-*n*-Butyl-2,3,6,7-tetramethoxyphenanthrene (8ag′). Colorless solid: mp 80−81 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 1.01 (t, J = 7.3 Hz, 3H), 1.47−1.57 (m, 2H), 1.75−1.86 (m, 2H), 3.05 (t, J = 7.4 Hz, 2H), 4.03 (s, 3H), 4.03 (s, 3H), 4.11 (s, 3H), 4.12 (s, 3H), 7.13 (s, 1H), 7.40 (s, 1H), 7.41 (s, 1H), 7.78 (s, 1H), 7.84 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 14.0 (CH_3), 22.8 (CH_2), 32.1 (CH_2), 33.1 (CH_2), 55.8 (2 × OCH_3), 56.0 (OCH_3), 56.1 (OCH_3), 102.8 (CH), 103.4 (CH), 104.8 (CH), 107.9 (CH), 123.4 (C_{quat}), 123.5 (CH), 124.9 (C_{quat}), 125.5 (C_{quat}), 126.5 (C_{quat}), 134.3 (C_{quat}), 148.4 (C_{quat}), 148.6 (2 × C_{quat}), 148.8 (C_{quat}); EI MS (70 eV), m/z (%) 354 (98) [M^+], 311 (100); HRMS (EI) calcd for $C_{22}H_{26}O_4$ 354.1831, found 354.1836.

9,10-Di-*n*-butyl-2,3,6,7-tetramethlyphenanthrene (8ba). Colorless solid: mp 82−83 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 1.03 (t, J = 7.1 Hz, 6H), 1.56−1.67 (m, 8H), 2.48 (s, 6H), 2.50 (s, 6H), 3.08 (t, J = 8.7 Hz, 4H), 7.79 (s, 2H), 8.40 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 14.1 (CH_3), 20.3 (CH_3), 20.5 (CH_3), 23.4 (CH_2), 28.8 (CH_2), 32.9 (CH_2), 123.1 (CH), 124.9 (CH), 127.9 (C_{quat}), 129.6 (C_{quat}), 132.4 (C_{quat}), 134.0 (C_{quat}), 134.9 (C_{quat}); EI MS (70 eV), m/z (%) 346 (55) [M^+], 261 (100); HRMS (EI) calcd for $C_{26}H_{34}$ 346.2661, found 346.2654.

9-*n*-Butyl-2,3,6,7-tetramethyl-10-phenylphenanthrene (8bb). Colorless solid: mp 155−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 0.81 (t, J = 7.3 Hz, 3H), 1.12−1.32 (m, 2H), 1.55−1.59 (m, 2H), 2.27 (s, 3H), 2.49 (s, 3H), 2.51 (s, 3H), 2.55 (s, 3H), 2.79 (t, J = 7.3 Hz, 2H), 7.00 (s, 1H), 7.27−7.30 (m, 2H), 7.44−7.52 (m, 3H), 7.85 (s, 1H), 8.43 (s, 1H), 8.48 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 13.8 (CH_3), 20.1 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 23.1 (CH_2), 30.0 (CH_2), 33.0 (CH_2), 122.5 (CH), 123.2 (CH), 125.3 (CH), 126.7 (CH), 127.4 (C_{quat}), 127.5 (CH), 128.2 (CH), 128.5 (C_{quat}), 129.1 (C_{quat}), 130.0 (CH), 130.7 (C_{quat}), 133.4 (C_{quat}), 134.5 (C_{quat}), 134.86 (C_{quat}), 134.89 (C_{quat}), 135.2 (C_{quat}), 135.5 (C_{quat}), 141.0 (C_{quat}); EI MS (70 eV), m/z (%) 366 (100) [M^+], 323 (57), 308 (55), 308 (55), 293 (42); HRMS (EI) calcd for $C_{28}H_{30}$ 366.2348, found 366.2338.

9-Cyclopropyl-2,3,6,7-tetramethyl-10-phenylphenanthrene (8bd). Colorless solid: mp 175−176 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 0.28−0.30 (m, 2H), 0.74−0.77 (m, 2H), 1.94−2.12 (m, 1H), 2.30 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 2.56 (s, 3H), 7.30 (s, 1H), 7.34−7.52 (m, 5H), 8.42 (s, 1H), 8.44 (s, 1H), 8.46 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 9.5 (2 × CH_2), 13.2 (CH), 20.2 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 122.5 (CH), 122.9 (CH), 126.4 (CH), 126.5 (CH), 127.1 (CH), 127.8 (2 × CH), 127.9 (C_{quat}), 128.2 (C_{quat}), 130.1 (C_{quat}), 131.1 (C_{quat}), 131.2 (2 × CH), 132.5 (C_{quat}), 134.8 (C_{quat}), 134.9 (C_{quat}), 137.5 (C_{quat}), 140.7 (C_{quat}). One C_{quat} cannot be observed due to signals overlap; EI MS (70 eV), m/z (%) 350 (64) [M^+], 335 (100) [$M^+ - CH_3$], 320 (46) [$M^+ - 2 \times CH_3$]; HRMS (EI) calcd for $C_{27}H_{26}$ 350.2035, found 350.2028.

2,7-Dibromo-9,10-di-*n*-butyl-3,6-dimethoxyphenanthrene (8da). Colorless solid: mp 167−168 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 1.04 (t, J = 7.1 Hz, 6H), 1.57−1.67 (m, 8H), 3.02 (t, J = 8.9 Hz, 4H), 4.11 (s, 6H), 7.85 (s, 2H), 8.23 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 14.0 (CH_3), 23.3 (CH_2), 28.9 (CH_2), 32.9 (CH_2), 56.4 (OCH_3), 103.8 (CH), 113.3 (C_{quat}), 127.5 (C_{quat}), 129.2 (C_{quat}), 129.8 (CH), 131.7 (C_{quat}), 153.4 (C_{quat}); EI MS (70 eV), m/z (%) 510/508/506 (25/100/27) [M^+], 425/423/421 (23/91/24); HRMS (EI) calcd for $C_{24}H_{28}Br_2O_2$ 508.0436, found 508.0432.

2,7-Dibromo-9-*n*-butyl-3,6-dimethoxy-10-phenylphenanthrene (8db). Colorless solid: mp 134−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 0.80 (t, J = 7.3 Hz, 3H), 1.23−1.28 (m, 2H), 1.50−1.55 (m, 2H), 2.72 (t, J = 7.1 Hz, 2H), 4.12 (s, 3H), 4.16 (s, 3H), 7.24 (s, 1H), 7.46−7.75 (m, 5H), 7.88 (s, 1H), 7.93 (s, 1H), 8.29 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 13.7 (CH_3), 23.0 (CH_2), 30.0 (CH_2), 30.1 (CH_2), 56.49 (OCH_3), 56.52 (OCH_3) 103.2 (CH), 103.8 (CH), 113.2 (C_{quat}), 113.6 (C_{quat}), 127.0 (C_{quat}), 127.4 (CH), 128.5 (CH), 128.6 (C_{quat}), 128.7 (C_{quat}), 130.0 (C_{quat}), 130.2 (CH), 130.4 (CH), 132.3 (CH), 132.7 (C_{quat}), 134.6 (C_{quat}), 139.5 (C_{quat}), 153.7 (C_{quat}), 154.0 (C_{quat}); EI MS (70 eV), m/z (%) 530/

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528/526 (28/100/29) [M^+], 406/404 (66/65); HRMS (EI) calcd for $C_{26}H_{24}Br_2O_2$ 528.0123, found 528.0117.

3,4,5,6-Tetramethoxy-9-phenyl-10-(*o*-tolyl)phenanthrene (8ei). Colorless solid: mp 163−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 1.95 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 3.99 (s, 6H), 6.91−7.25 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$, plus DEPT, ppm) δ = 20.0 (CH_3), 56.81 (OCH_3), 56.84 (OCH_3), 60.9 (2 × OCH_3), 113.6 (CH), 120.9 (CH), 120.5 (CH), 122.3 (C_{quat}), 122.5 (C_{quat}), 125.1 (CH), 126.4 (CH), 126.9 (CH), 127.4 (CH), 127.6 (CH), 128.6 (C_{quat}), 129.3 (C_{quat}), 129.4 (CH), 129.6 (CH), 131.1 (CH), 131.5 (CH), 134.0 (C_{quat}), 134.4 (C_{quat}), 136.9 (C_{quat}), 138.9 (C_{quat}), 139.5 (C_{quat}), 147.7 (C_{quat}), 150.78 (C_{quat}), 150.84 (C_{quat}). One CH and one C_{quat} cannot be observed due to signals overlap; EI MS (70 eV), *m*/*z* (%) 464 (100) [M^+], 418 (13); HRMS (EI) calcd for $C_{31}H_{28}O_4$ 464.1988, found 464.1982.

9-*n*-Butyl-2,3-dimethoxy-10-phenylphenanthrene (8gb-I). Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 0.81 (t, *J* = 7.3 Hz, 3H), 1.26−1.35 (m, 4H), 2.81−2.85 (m, 2H), 3.68 (s, 3H), 4.11 (s, 3H), 6.67 (s, 1H), 7.31−7.34 (m, 2H), 7.44−7.54 (m, 3H), 7.59−7.66 (m, 2H), 8.06 (s, 1H), 8.14 (d, ^3J = 8.0 Hz, 1H), 8.62 (d, ^3J = 8.4 Hz, 1H); ^{13}C NMR (A mixture of **8gb**-I and **8gb**-II, 100 MHz, $CDCl_3$, plus DEPT, ppm) δ = 13.7 (CH_3), 23.1 (CH_2), 29.7 (CH_2), 30.1 (CH_2), 30.3 (CH_2), 32.6 (CH_2), 33.1 (CH_2), 55.4 (OCH_3), 56.0 (OCH_3), 103.0 (CH), 103.7 (CH), 105.6 (CH), 107.9 (CH), 121.8 (CH), 122.5 (CH), 123.9 (C_{quat}), 125.3 (CH), 125.6 (CH), 125.7 (CH), 126.9 (CH), 127.0 (CH), 127.5 (C_{quat}), 127.6 (CH), 128.2 (CH), 128.3 (CH), 129.8 (C_{quat}), 130.1 (CH), 130.2 (C_{quat}), 130.4 (CH), 133.1 (C_{quat}), 136.2 (C_{quat}), 140.7 (C_{quat}), 148.6 (C_{quat}), 148.8 (C_{quat}); EI MS (70 eV), *m*/*z* (%) 370 (100) [M^+], 327 (37), 296 (36), 191 (41); HRMS (EI) calcd for $C_{26}H_{26}O_2$ 370.1933, found 370.1933.

***tert*-Butyl 2-[(2,3,6,7-tetramethoxyphenanthrene-9-yl)-methyl]piperidine-1-carboxylate (8ak).** Colorless solid: mp 162−163 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 1.20 (brs, 9H), 1.41−1.89 (m, 7H), 3.09 (dd, *J* = 12.9, 2.1 Hz, 1H), 3.21−3.35 (m, 2H), 4.02 (s, 3H), 4.10 (s, 3H), 4.12 (s, 3H), 4.14 (s, 3H), 4.67−4.78 (m, 1H), 7.15 (s, 1H), 7.34 (s, 1H), 7.77 (s, 1H), 7.75−7.83 (m, 1H), 7.83 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 18.9 (CH_2), 25.6 (CH_2), 28.1 (CH_3), 34.0 (CH_2), 39.4 (CH_2), 50.2 (CH), 55.8 (OCH_3), 56.0 (OCH_3), 56.1 (OCH_3), 56.3 (OCH_3), 79.9 (C_{quat}), 102.8 (CH), 103.3 (CH), 105.6 (CH), 107.9 (CH), 123.8 (C_{quat}), 124.9 (C_{quat}), 125.2 (CH), 125.9 (C_{quat}), 126.2 (C_{quat}), 131.2 (C_{quat}), 148.72 (C_{quat}), 148.84 (C_{quat}), 148.88 (C_{quat}), 148.90 (C_{quat}), 155.0 (C_{quat}). One CH_2 was not observed due to signals overlap; EI MS (70 eV), *m*/*z* (%) 495 (5) [M^+], 312 (80), 128 (75), 84 (100); HRMS (EI) calcd for $C_{29}H_{37}NO_6$ 495.2621, found 495.2615.

(*S*)-(+)-*tert*-Butyl 2-[(3,6-dimethoxyphenanthren-9-yl)-methyl]pyrrolidine-1-carboxylate [(*S*)-8cj]. Colorless solid: mp 121−22 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 1.56 (s, 9H), 1.61−1.71 (m, 1H), 1.74−1.87 (m, 2H), 1.90−2.06 (m, 1H), 2.72 (dd, *J* = 13.2, 10.6 Hz, 1H), 3.34−3.53 (m, 2H), 3.68−3.81 (m, 1H), 4.01 (s, 3H), 4.02 (s, 3H), 4.22−4.34 (m, 1H), 7.17−7.32 (m, 2H), 7.34 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.93 (s, 1H), 7.99 (d, *J* = 1.8 Hz, 1H), 8.29−8.47 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 22.7 (CH_2), 28.7 (CH_3), 29.3 (CH_2), 38.1 (CH_2), 46.0 (CH_2), 55.52 (OCH_3), 55.54 (OCH_3), 57.1 (CH), 79.5 (C_{quat}), 104.3 (CH), 104.9 (CH), 116.1 (CH), 116.6 (CH), 125.5 (CH), 126.4 (C_{quat}), 127.0 (CH), 129.5 (CH), 130.5 (C_{quat}), 131.2 (C_{quat}), 131.5 (C_{quat}), 154.7 (C_{quat}), 157.8 (C_{quat}). Two C_{quat} was not observed due to signals overlap; EI MS (70 eV), *m*/*z* (%) 421 (14) [M^+], 251 (83), 114 (70), 70 (100); HRMS (EI) calcd for $C_{26}H_{31}NO_4$ 421.2253, found 421.2258. $[\alpha]^{20}_D$ +4.9 (*c* 0.138, CH_2Cl_2).

***tert*-Butyl 2-[(3,6-dimethoxyphenanthren-9-yl)methyl]-piperidine-1-carboxylate (8ck).** Colorless solid: mp 121−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 1.20 (br s, 9H), 1.40−1.67 (m, 4H), 1.70−1.86 (m, 2H), 3.09 (dd, *J* = 13.2, 2.9 Hz, 1H), 3.24 (dd, *J* = 13.6, 8.5 Hz, 1H), 3.31 (dd, *J* = 13.6, 7.0 Hz, 1H), 4.00 (s, 3H), 4.02 (s, 3H), 4.15 (d, *J* = 12.1 Hz, 1H), 4.63−4.73 (m, 1H), 7.21 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.29 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.34 (s, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.92 (d, *J* = 2.1 Hz, 1H), 8.00 (d, *J* = 2.5 Hz, 1H), 8.18 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, plus DEPT, ppm) δ = 18.9 (CH_2), 22.5 (CH_2), 27.3 (CH_2), 28.2 (CH_3), 33.6 (CH_2), 38.8 (CH_2), 50.6 (CH), 55.5 (2 × OCH_3), 79.1 (C_{quat}), 104.2 (CH), 105.0 (CH), 116.2 (CH), 116.5 (CH), 125.1 (CH), 126.3 (CH), 126.4 (C_{quat}), 127.0 (C_{quat}), 129.6 (CH), 130.5 (C_{quat}), 130.9 (C_{quat}), 131.6 (C_{quat}), 155.0 (C_{quat}), 157.76 (C_{quat}), 157.81 (C_{quat}); EI MS (70 eV), *m*/*z* (%) 435 (100) [M^+], 362 (58), 334 (19); HRMS (EI) calcd for $C_{27}H_{33}NO_4$ 435.2410, found 435.2406.

(*S*)-(+)-*tert*-Butyl 2-[(3,4,5,6-tetramethoxyphenanthrene-9-yl)methyl]pyrrolidine-1-carboxylate [(*S*)-8ej, two diastereomers]. Pale yellow oil: ^{1}H NMR (400 MHz, CD_2Cl_2, ppm) 1.53 (s, 9H), 1.55 (s, 9H), 1.64−1.74 (m, 2H), 1.71−1.82 (m, 4H), 1.92−2.04 (m, 2H), 2.60−2.73 (m, 2H), 3.28−3.59 (m, 6H), 3.67 (s, 6H), 3.71 (s, 6H), 4.00 (s, 6H), 4.03 (s, 6H), 4.19−4.36 (m, 2H), 7.19 (s, 2H), 7.31 (d, *J* = 8.5 Hz, 3H), 7.44 (d, *J* = 8.5 Hz, 3H), 7.97 (d, *J* = 8.5 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2, plus DEPT, ppm) δ = 21.9 (CH_2), 22.8 (CH_2), 27.8 (CH_3), 27.9 (CH_3), 28.4 (CH_2), 29.1 (CH_2), 36.8 (CH_2), 37.4 (CH_2), 45.8 (CH_2), 46.2 (CH_2), 56.0 (CH), 56.1 (OCH_3), 56.2 (OCH_3), 56.5 (CH), 58.87 (OCH_3), 59.94 (OCH_3), 78.1 (C_{quat}), 78.7 (C_{quat}), 112.6 (CH), 112.9 (CH), 113.5 (CH), 118.3 (CH), 118.8 (CH), 120.8 (CH), 120.9 (CH), 121.4 (C_{quat}), 122.7 (C_{quat}), 125.1 (CH), 125.6 (CH), 127.8 (C_{quat}), 128.3 (C_{quat}), 130.5 (C_{quat}), 130.8 (C_{quat}), 147.2 (C_{quat}), 147.3 (C_{quat}), 147.5 (C_{quat}), 150.3 (C_{quat}) 153.8 (C_{quat}) 154.0 (C_{quat}); EI MS (70 eV), *m*/*z* (%) 481 (100) [M^+], 408 (20); HRMS (EI) calcd for $C_{28}H_{35}NO_6$ 481.2464, found 481.2451. $[\alpha]^{20}_D$ +30.7 (*c* 0.021, MeOH).

(*S*)-(+)-*tert*-Butyl 2-[(1,2,3,6,7,8-hexamethoxyphenanthrene-9-yl)methyl]pyrrolidine-1-carboxylate [(*S*)-8fj, two diastereomers]. Pale yellow oil: ^{1}H NMR (400 MHz, CD_2Cl_2, ppm) 0.81 (br s, 9H), 1.61−1.80 (m, 2H), 1.83−1.91 (m, 1H), 1.96−2.05 (m, 1H), 3.01−3.08 (m, 1H) 3.34−3.46 (m, 2H), 3.53−3.62 (m, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 3.98 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 4.30−4.41 (m, 1H), 7.53 (br s, 1H), 7.60 (s, 1H), 7.71 (s, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2, plus DEPT, ppm) δ = 22.7 (CH_2), 23.5 (CH_2), 27.4 (CH_3), 28.1 (CH_3), 40.0 (CH_2), 40.14 (CH_2), 41.07 (CH_2), 45.35 (CH_2), 46.3 (CH_2), 55.8 (OCH_3), 56.0 (OCH_3), 58.3 (OCH_3), 58.9 (OCH_3), 60.6 (OCH_3), 60.9 (OCH_3), 61.3 (OCH_3), 61.5 (OCH_3), 77.8 (C_{quat}), 99.3 (CH), 100.2 (CH), 121.46 (CH), 121.59 (C_{quat}), 121.67 (C_{quat}), 125.7 (C_{quat}), 127.7 (C_{quat}), 131.2 (C_{quat}), 141.4 (C_{quat}), 142.4 (C_{quat}), 148.2 (C_{quat}), 151.4 (C_{quat}), 152.2 (C_{quat}), 152.6 (C_{quat}), 154.3 (C_{quat}); EI MS (70 eV), *m*/*z* (%) 541 (11) [M^+], 371 (21), 57 (100); HRMS (EI) calcd for $C_{30}H_{39}NO_8$ 541.2676, found 541.2673. $[\alpha]^{20}_D$ +2.6 (*c* 0.121, MeOH).

***tert*-Butyl 2-[(2,3,6-trimethoxyphenanthren-9-yl)methyl]-piperidine-1-carboxylate (8hk-II).** Pale yellow solid: mp 160−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ = 1.16 (br s, 9H), 1.39−1.62 (m, 4H), 1.69−1.80 (m, 2H), 3.08 (td, *J* = 13.2, 2.6 Hz, 1H), 3.23 (dd, *J* = 13.7, 8.1 Hz, 1H), 3.31 (dd, *J* = 13.7, 7.0 Hz, 1H), 4.02 (s, 3H), 4.03 (s, 3H), 4.10 (s, 3H), 4.14−4.20 (m, 1H), 4.64−4.74 (m, 1H), 7.15 (s, 1H), 7.24 (dd, *J* = 7.6, 2.3 Hz, 1H), 7.30 (s, 1H), 7.85 (s, 1H), 7.91 (d, *J* = 2.3 Hz, 1H), 8.16 (br d, *J* = 7.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, plus DEPT, ppm) δ = 19.0 (CH_2), 25.6 (CH_2), 27.5 (CH_2), 28.1 (CH_3), 33.7 (CH_2), 38.8 (CH_2), 50.6 (CH), 55.5 (OCH_3), 55.8 (OCH_3), 56.0 (OCH_3), 79.1 (C_{quat}), 103.3 (CH), 104.6 (CH), 107.9 (CH), 115.0 (CH), 123.7 (C_{quat}), 124.6 (CH), 125.4 (C_{quat}), 126.3 (CH), 127.4 (C_{quat}), 131.65 (C_{quat}), 131.70 (C_{quat}), 148.7 (C_{quat}), 149.5 (C_{quat}), 155.0 (C_{quat}), 157.8 (C_{quat}); EI MS (70 eV), *m*/*z* (%) 465 (2) [M^+], 281 (20), 185 (10), 128 (58), 57 (100); HRMS (EI) calcd for $C_{28}H_{35}NO_5$ 465.2515, found 465.2521.

Preparation of Phenanthroindolizidine and Phenanthroquinolizidine Alkaloids from Phenanthrenes by the Pictet−Spengler Reaction. According to the procedure developed by Herr and co-workers,[5e] phenanthrenes **8aj**, **8ej** and **8hk**-II were transformed to alkaloids **1**, **10**, and **5**, respectively. The reactions were conducted on a 0.20 mmol scale. ^{1}H NMR spectra of **1**[5a,g] and **5**[5n] are identical to those previously reported in literatures.

(+)-(13a*S*)-9,11,12,13,13a,14-Hexahydro-3,4,5,6-tetramethoxydibenzo[*f*,*h*]pyrrolo[1,2-*b*]isoquinoline [(+)-10]. Colorless solid: mp 82−83 °C; ^{1}H NMR (300 MHz, DMSO-d_6, CF_3CO_2H, ppm) δ = 1.56−1.74 (m, 1H), 1.77−1.96 (m, 2H), 2.08−2.23 (m, 1H), 2.26−2.42 (m, 2H), 2.66−2.83 (m, 1H), 3.14−3.26 (m,

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1H), 3.45−3.56 (m, 2H), 3.62 (s, 3H), 3.63 (s, 3H), 3.96 (s, 6H), 4.42 (d, J = 15.6 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H); ^{1}H NMR (500 MHz, CD_2Cl_2, ppm) δ = 1.65−1.73 (m, 1H, 13-H), 1.84−1.91 (m, 1H, 12-H), 1.92−2.01 (m, 1H, 12-H), 2.15−2.22 (m, 1H, 13-H), 2.37 (q, J = 8.8 Hz, 1H, 11-H), 2.40−2.44 (m, 1H, 13a-H), 2.81 (dd, J = 15.5, 11.0 Hz, 1H, 14-H), 3.20 (dd, J = 15.5, 1.5 Hz, 1H, 14-H), 3.36 (td, J = 8.8, 2.0 Hz, 1H, 11-H), 3.56 (d, J = 15.0 Hz, 1H, 9-H), 3.63 and 3.64 (each s and 3H, 4,5-OCH_3), 3.98 and 3.99 (each s and 3H, 3,6-OCH_3), 4.42 (d, J = 15.0 Hz, 1H, 9-H), 7.28 (d, J = 9.0 Hz, 1H, 7-H), 7.30 (d, J = 9.0 Hz, 1H, 2-H), 7.45 (d, J = 9.0 Hz, 1H, 8-H), 7.60 (d, J = 9.0 Hz, 1H, 1-H); ^{13}C NMR (125 MHz, CD_2Cl_2, plus DEPT, ppm) δ = 11.8 (C-12), 21.4 (C-13), 23.7 (C-14), 44.1 (C-9), 45.2 (C-11), 46.8 and 46.9 (3,6-OCH_3), 50.5 (C-13a), 50.8 (4,5-OCH_3), 103.7 (C-7), 103.8 (C-2), 106.2 (C-8), 107.2 (C-1), 112.0 (C-4b), 112.2 (C-4a), 116.5 (C-8b), 116.8 (C-14a), 117.4 (C-8a), 118.7 (C-14b), 138.1 (C-4), 138.3 (C-5), 140.7 (C-3), 140.8 (C-6); EI MS (70 eV), m/z (%) 393 (31) [M^+], 324 (100); HRMS (EI) calcd for $C_{24}H_{27}NO_4$ 393.1940, found 393.1933. $[\alpha]^{20}_D$ +17.5 (c 0.032, MeOH).

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectral data of all new compounds, **5**, **8aj** and **8hk**-I. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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