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Total Synthesis of Aristolactams via a One-Pot Suzuki−Miyaura Coupling/Aldol Condensation Cascade Reaction

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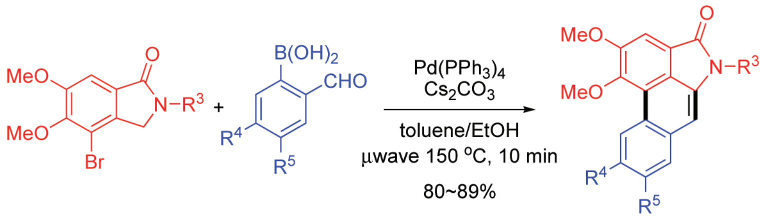
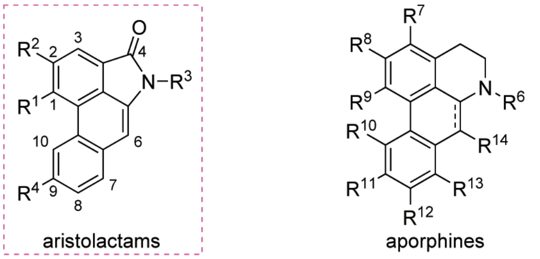
ABSTRACT



A direct one-pot synthesis of phenanthrene lactams, which employs a Suzuki−Miyaura coupling/aldol condensation cascade reaction of isoindolin-1-one with 2-formylphenylboronic acid, has been developed. The approach is used to efficiently produce a number of natural aristolactams, such as aristolactam BII (cepharanone B), aristolactam BIII, aristolactam FI (piperolactam A), *N*-methyl piperolactam A, and sauristolactam.

Aristolactams belong to a large and important family of naturally occurring alkaloids that possess the phenanthrene lactam skeleton (Figure 1).[1] The aristolactams and the structurally related aporphines are mainly isolated from plant species, such as *Aristolochiaceae*,[2] *Annonaceae*,[3] *Piperaceae*,[4] and *Saururaceae*.[5] Traditionally, the aristolactams have been used as folk medicines in Eastern Asia.[6] In this regard, they possess an interesting array of biological



Aristolactam BII (**1**); R^1 = R^2 = OMe, R^3 = R^4 = H
Aristolactam BIII (**2**); R^1 = R^2 = R^4 = OMe, R^3 = H
Aristolactam FI (**3**); R^1 = OH, R^2 = OMe, R^3 = R^4 = H
N-Methyl piperolactam A (**4**); R^1 = OH, R^2 = OMe, R^3 = Me, R^4 = H
Sauristolactam (**5**); R^1 = OMe, R^2 = OH, R^3 = Me, R^4 = H

Figure 1. Aristolactam and aporphine analogues.

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properties including anticancer,[2b,2c,7] anti-inflammatory,[3b,3c] antiplatelet,[3a,4a] and neuro-protective[5a] activities. For example, aristolactam BII (cepharanone B, **1**)[3c] has been shown to inhibit T and B lymphocyte proliferation as well as displaying cytotoxic activity, while aristolactam FI (piperolactam A, **3**)[5a] displays inhibitory effects on NO generation by RAW264.7 macropharges in response to lipopolysaccharides. Although the cytotoxicity of aristolactams is well-known, structure−activity relationships have not been explored mainly as a consequence of the synthetic difficulties associated with preparing a diverse array of aristolactam analogues.

Considerable effort has been devoted to the synthesis of aristolactams.[8] For example, in pioneering studies, Castedo explored inter- and intramolecular benzyne cycloadditions of enamides, photochemical cyclizations of iodostilbenic precursors, and lactone ring contractions of dibenzochromanones.[9] Couture has also developed an approach to the construction of phenanthrene lactams that relies on aryne-mediated cyclization of a phosphorylated amino carbanion followed by sequential Horner reaction and radical cyclization.[10]

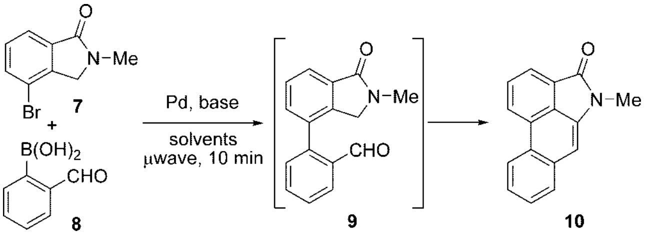
In a previous report,[11] we described a strategy for the direct one-pot synthesis of phenanthrenes that employs a Suzuki−Miyaura coupling/aldol condensation cascade sequence. Here we report the application of this procedure to the total synthesis of aristolactams, including aristolactam BII, aristolactam BIII, aristolactam FI, *N*-methyl piperolactam A, and sauristolactam. In addition, we have synthesized several unnatural aristolactam analogues.

A crucial feature of the new synthetic strategy arises from the recognition that phenanthrene lactam (**I**) can be synthesized from the reaction of 4-bromoisoindolin-1-one (**II**) with 2-formylarylboronic acid (**III**) via a Suzuki−Miyaura coupling/aldol-type condensation cascade reaction (Scheme 1). Moreover, the key intermediate, 4-bromoisoindolin-1-one (**II**) derives from commercially available 3,4-dimethoxytoluene (**6**) via several straightforward functional group transformations.

Scheme 1. Construction of a Phenanthrene Lactam via Suzuki−Miyaura Coupling/Aldol Condensation Cascade Reaction

Our protocol was first examined by using a direct one-pot cascade reaction of 4-bromoisoindolin-1-one **7**[12] with 2-formylphenylboronic acid (**8**) under typical Suzuki−Miyaura coupling[13] conditions promoted by microwave irradiation.[14] The results of this exploratory study are illustrated in Table 1. Among the various palladium catalysts examined, $Pd(PPh_3)_4$ was found to be the most effective, affording phenanthrene lactam **10** in 50% yield along with the intermediate, biphenyl **9**, in 15% yield (entry 3). When the reaction temperature was increased to 170 °C, **10** was obtained in an improved 88% yield with complete consumption of biphenyl **9** (entry 4). After considerable experimenta-

Table 1. Direct One-Pot Synthesis of Phenanthrene Lactam **10**[a]



entry	Pd	base	solvents	temp (°C)	yield (%)[b] 9	yield (%)[b] 10
1	$Pd(OAc)_2$	Cs_2CO_3	dioxane	150	0	7
2	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	dioxane	150	90	0
3	$Pd(PPh_3)_4$	Cs_2CO_3	dioxane	150	15	50
4	$Pd(PPh_3)_4$	Cs_2CO_3	dioxane	170[e]	0	88
5	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	170[e]	30	6
6	$Pd(PPh_3)_4$	Cs_2CO_3	dioxane/ H_2O[c]	150	62	6
7	**$Pd(PPh_3)_4$**	**Cs_2CO_3**	**toluene/ EtOH**[d]	**150**	**0**	**99**
8	$Pd(PPh_3)_4$	K_3PO_4	toluene/ EtOH[d]	150	0	89
9	$Pd(PPh_3)_4$	Na_2CO_3	toluene/ EtOH[d]	150	47	0

[a] Reaction conditions: isoindolinone **7** (0.5 mmol), boronic acid **8** (0.6 mmol, 1.2 equiv), Pd (4 mol %), base (1.5 mmol), solvents (3 mL), microwave, 10 min. [b] Isolated yield. [c] Dioxane/H_2O = 2.7/0.3 mL. [d] Toluene/EtOH = 2/1 mL. [e] Microwave heating for 20 min.

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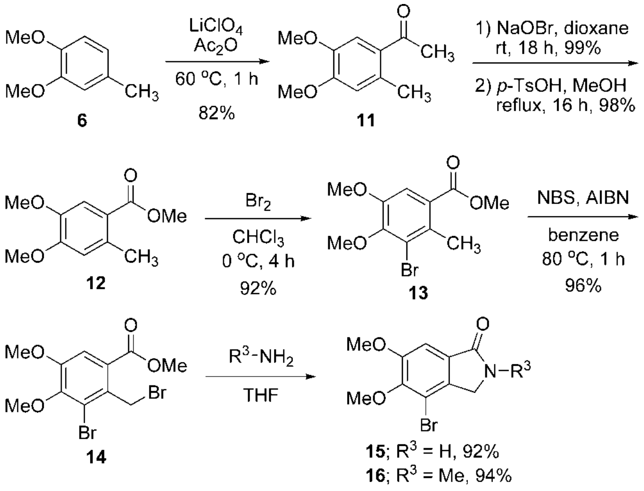
tion, probing various solvents and bases, we observed that the reaction of isoindolone **7** with boronic acid **8**, in the presence of $Pd(PPh_3)_4$ (4 mol %) and Cs_2CO_3 (3 equiv) in toluene/EtOH (2:1 v/v) at 150 °C under microwave irradiation, gave phenanthrene lactam **10** in near quantitative yield (entry 7).

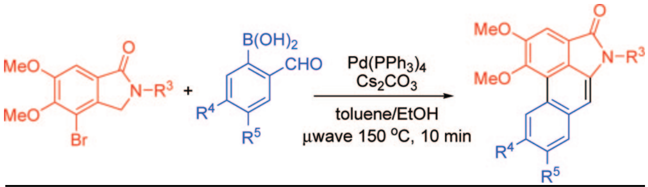
With optimized conditions for the direct one-pot synthesis of phenanthrene lactam **10** in hand, we next investigated the total synthesis of aristolactams. The preparation of the requisite isoindolin-1-ones, **15** and **16**, began with commercially available 3,4-dimethoxytoluene (Scheme 2). Modified Friedel−Crafts acetylation of **6** with acetic anhydride readily afforded acetophenone **11** in 82% yield.[15] Oxidation of **11** to form the corresponding carboxylic acid followed by acid-catalyzed esterification with methanol provided methyl benzoate **12** in quantitative yield.[16] Next, 3-bromo-2-(bromomethyl)benzoate **14** was prepared by a two-step bromination sequence using bromine followed by *N*-bromosuccinimide. Lactamization of **14** with aqueous ammonia led to the isoindolone **15** in 92% yield, while reaction of **14** with methylamine gave isoindolone **16** in a better 94% yield.

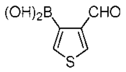
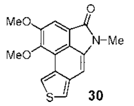
Scheme 2. Preparation of Isoindolin-1-ones



With the key intermediates **15** and **16** in hand, we explored the direct one-pot synthesis of aristolactam analogues using various 2-formylphenylboronic acids. The results are illustrated in Table 2. Using the optimized conditions ($Pd(PPh_3)_4$, Cs_2CO_3, toluene/EtOH, microwave 150 °C, 10 min), isoindolone **15** reacted with boronic acids **8** and **17** to furnish the respective aristolactam BII (cepharanone B, **1**) and aristolactam BIII (**2**) in 81% and 83% yields (entries 1 and 2). To the best of our knowledge, this approach to aristolactams BII and BIII (from commercially available 3,4-dimethoxytoluene in seven steps and 52∼54% overall yield) is one of the shortest and most efficient developed to date. In addition, the reactions of *N*-methyl isoindolone **16** with various boronic acids, **8** and **18**−**22**, proceeded smoothly to provide the corresponding phenanthrene lactams **24**−**29** in 80−89% yields (entries 3−8). It is worth mentioning that 2-formylphenylboronic acids, possessing electron-deficient or -rich substituents, are reactive in the cascade process. However, the reaction with 3-thienylboronic acid **23** was less effective, giving the lactam **30** in only a 35% yield (entry 9).

Table 2. Synthesis of Aristolactam Analogues[a]



entry	R^3	boronic acid			product	yield
		R^4	R^5			(%)[b]
1	H (**15**)	H	H	(**8**)	Aristolactam BII (**1**)	81
2	H (**15**)	OMe	H	(**17**)	Aristolactam BIII (**2**)	83
3	Me (**16**)	H	H	(**8**)	**24**	86
4	Me (**16**)	OMe	OMe	(**18**)	**25**	86
5	Me (**16**)	OCH_2O		(**19**)	**26**	80
6	Me (**16**)	H	OMe	(**20**)	**27**	89
7	Me (**16**)	H	Cl	(**21**)	**28**	86
8	Me (**16**)	Me	H	(**22**)	**29**	82
9	Me (**16**)			(**23**)	 **30**	35

[a] Reaction conditions: isoindolinone (0.5 mmol), boronic acid (0.6 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (4 mol %), Cs_2CO_3 (1.5 mmol, 3.0 equiv), toluene/EtOH (2 mL/1 mL), microwave 150 °C, 10 min. [b] Isolated yield.

Hydroxyl-containing aristolactams can be formed by regioselective cleavage of aryl−methyl ether groups. For example, aristolactam FI (piperolactam A, **3**) and *N*-methyl piperolactam A (**4**) are obtained in satisfactory yields via the selective monodemethylation of the C-1 positions of **1** and **24** using LiCl in DMF (Scheme 3).[17] Regioselective demethylation at the C-2 position of **24**, however, was

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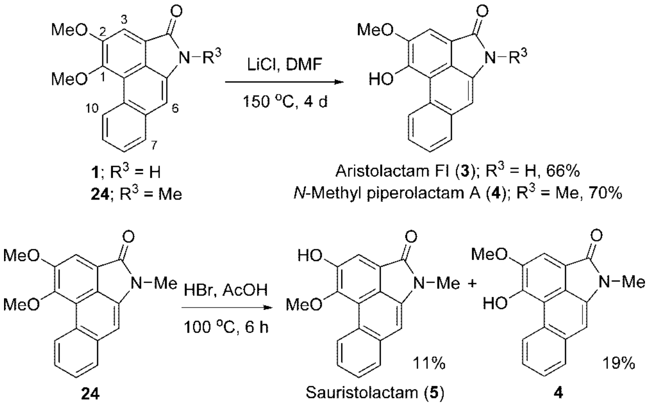
Scheme 3. Demethylation for Aristolactams



unsuccessful using other reported methods.[18] By using HBr/AcOH conditions, both sauristolactam (**5**) and **4** were obtained in 11% and 19% yields, respectively, along with a large amount of dihydroxy product.

Surprisingly, during comparison of the ^{1}H NMR spectra for aristolactam FI, we found that the reported data by Desai[4c] and Cassady[19] did not match each other. Indeed, the spectral data originally assigned to aristolactam AII (**31**),[2d,20] the regioisomer of aristolactam FI, did not match with those for our synthetic compound **3**.[21] The observed ^{1}H NOE data of **3** were fully consistent with the configurational assignment of aristolactam FI as shown in Figure 2. Thus, we were finally able to unequivocally reassign the structures of aristolactam FI and aristolactam AII.

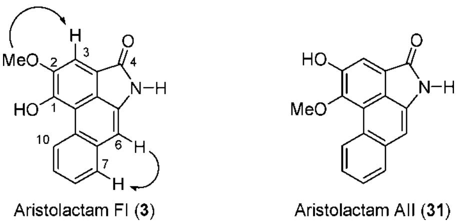
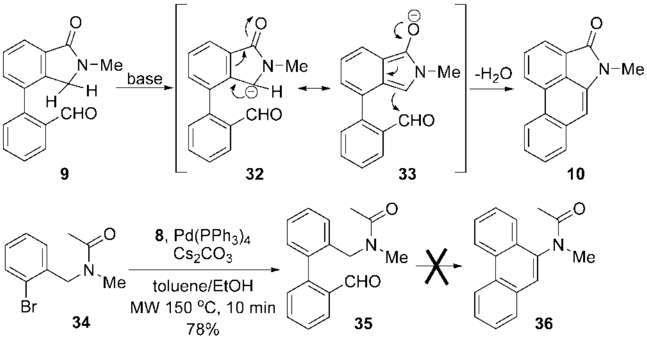


Figure 2. Observed NOE of aristolactam FI and the structure of aristolactam AII.

As shown in Scheme 4, the acidity of the methylene protons at C-3 of isoindolin-1-one **9** is crucial for operation of the aldol condensation process.[10c] This is exemplified by the observation that acetamide **35** does not participate in the aldol condensation to provide the corresponding phenanthrene **36**.[11] Therefore, it is reasonable to hypothesize that formation of isoindolin-1-one enolate **33** influences the one-pot cascade reaction under the given basic conditions.

Scheme 4. Plausible Mechanism for Aldol Condensation



In summary, we have successfully demonstrated that aristolactams can be prepared in excellent yields by using a direct one-pot Suzuki−Miyaura coupling/aldol-type cascade process to construct the core phenanthrene ring system. By employing this strategy, several natural aristolactams, including aristolactam BII (cepharanone B), aristolactam BIII, aristolactam FI (piperolactam A), *N*-methyl piperolactam A, and sauristolactam, have been prepared. Furthermore, a number of unnatural aristolactam derivatives have been generated in this manner with high efficiency. The structure of aristolactam FI was ambiguously confirmed based on this concise synthesis of the natural product. Full details of studies involving the construction of an aristolactam library and determination of their biological activities will be reported in due course.

Acknowledgment. We thank the KRICT and the Ministry of Science and Technology, Korea (KN-0713), for financial support. We are grateful to Prof. S. H. Sung (Seoul Natl. Univ.) for providing ^{1}H NMR spectra of natural aristolactam AII and sauristolactam.

Supporting Information Available: Experimental procedures and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] See Supporting Information for the comparison of ^{1}H NMR chemical shifts of aristolactam FI, AII, *N*-methyl piperolactam A, and sauristolactam (Table S1).