

Modular Syntheses of Phenanthroindolizidine Natural Products

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Supporting Information



ABSTRACT: A highly concise strategy for the total synthesis of phenanthroindolizidines was developed. The one-pot iterative Suzuki-Miyaura reaction of aryl boronic acids with ortho-bromoaryl N-methyliminodiacetate (MIDA) boronate followed by a second Suzuki-Miyaura reaction with a suitable pyridyl bromide provided ortho-aza-terphenyls. Subsequent saturation of the triple bond, treatment with mesyl chloride, and reduction of the resulting dihydroindolizidinium ring afforded the hexahydroindolizines. A final vanadium-catalyzed oxidative electrocyclization provided the desired alkaloids in only three column-separation operations.

nspired by nature's efficient synthesis of organic molecules via building block-based pathways, chemists have developed novel synthetic routes for biologically important compounds based on analogous building block-based strategies.¹⁷ These approaches can significantly simplify the process of organic synthesis by eliminating the need for investigation and optimization of customized reaction sequences. Among the building block strategies developed, the iterative Suzuki-Miyaura reaction has attracted considerable attention² because (1) this coupling reaction displays a very broad substrate scope and (2) several approaches for modulating the reactivities of building blocks have been developed.^{3,4} Furthermore, several excellent examples of total syntheses of biologically important natural products via the iterative Suzuki-Miyaura reaction have been recently reported.⁵

Despite the apparent advantages of the iterative Suzuki-Miyaura reaction in the synthesis of biologically important molecules, there is further room for improvement. The preparation of building blocks, such as halogenated boronic acid derivatives with modulated reactivity of the boronic acid functionality, is one of the key challenges. Conventionally, these building blocks are prepared from dihalogenated compounds via chemoselective installation of a boronic acid functional group at the more reactive halogen, followed by protection of the boronic acid functional group.⁶ However, this approach generally requires a relatively lengthy sequence and/

or chemoselectivity during the borylation step, often leading to low yields of the desired products.

To overcome this problem, we recently developed a highly efficient protocol for the preparation of halogenated Nmethyliminodiacetate (MIDA) boronates,⁷ which is a class of building blocks for the iterative Suzuki-Miyaura reaction, via direct halogenation of aryl MIDA boronates using the MIDA boronate moiety as the blocking group in the halogenation reactions.^{8,9} Furthermore, we successfully developed highly efficient total syntheses of dictyoterphenyls A and B via an iterative Suzuki-Miyaura strategy using these building blocks. As part of our research program on the development of efficient synthetic routes for biologically important natural products via iterative Suzuki-Miyaura coupling with these building blocks, we herein disclose highly concise total syntheses of phenanthroindolizidine natural products.

Since phenanthroindolizidine alkaloids have interesting biological activities,¹⁰ such as anticancer, anti-inflammatory, antiasthmatic, and antilupus activities, they have received considerable attention from synthetic and medicinal communities.¹¹ In addition to their biological activities, these natural products display structural diversity; in particular, they possess a different number of methoxy groups at different positions in

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Figure 1. Structures of Representative Phenanthroindolizidine Alkaloids

the phenanthrene ring (Figure 1). Thus, although numerous total syntheses of these natural products have been reported in the past decades, 11,12 there have been few general synthetic approaches that cover the structural diversity found in phenanthroindolizidine natural products.¹³

Although these natural products apparently possess structural diversity, we noticed that they exhibit structural similarity. First, despite variation in the number and position of methoxy groups in the phenanthrene ring, one of the phenyl rings in the phenanthrene ring has two methoxy groups at the 1,2-positions, i.e., the A-ring in these natural products (highlighted with a green box in Figure 1). Second, all the phenanthroindolizidine alkaloids possess an A,C-ring-linked biphenyl scaffold bearing an indolizidine ring at the 2-position of the A-ring (the skeleton was highlighted with a blue line in Figure 1), although the position of the nitrogen atom in the indolizidine ring differs in the different alkaloids; the natural products in Group A bear the biphenyl ring at the para position relative to the nitrogen in the indolizidine moiety, while natural products in group B carry the biphenyl scaffold linked at the meta position relative to the nitrogen in the indolizidine moiety.

Considering these structural similarities, we hypothesized that all the phenanthroindolizidines could be synthesized from the corresponding aza-ortho-terphenyl compounds (7, Scheme 1), if the pyridyl ring in the aza-ortho-terphenyl scaffold could be used as a precursor for the piperidine ring in the indolizidine ring.¹⁴ Based on this hypothesis, we depict the retrosynthetic analysis of the phenanthroindolizidines in Scheme 1. Phenanthroindolizidine natural products could be prepared via the B-ring formation from dihydroindolizidinium salts 6,15 which could be prepared from linear aza-orthoterphenyls 7 via E-ring formation. Linear aza-ortho-terphenyl compounds 7 could be prepared via an iterative Suzuki-Miyaura coupling reaction of an aryl boronic acid 8 carrying a methoxy group(s) at a suitable position, bifunctional orthobromoaryl MIDA boronate 9, and a suitable pyridyl bromide 10 that has a propargyl alcohol substituent in the ortho position. Notably, this linear-to-cyclized approach^{5f} would allow this complex all-fused pentacyclic natural product skeleton to be accessed in a manner that leverages the many advantageous features of building-block-based synthesis.

With this retrosynthetic analysis in mind, the synthesis began with the preparation of building blocks 9 and 10 (Scheme 2). Brominated aryl MIDA boronate 9 was prepared in a 94% yield from boronic acid 8a via MIDA boronate





Scheme 2. Preparation of Building Blocks 9 and 10



formation, followed by the direct bromination using a MIDA boronate moiety as a blocking group (Scheme 2a).⁹ Furthermore, pyridyl bromides **10** could be prepared via the regioselective Sonogashira coupling reaction of a suitable dibromopyridine **11** with propargyl alcohol (Scheme 2b).^{16,17}

With these building blocks in hand, we first attempted to synthesize tylophorine (1), antofine (2), and tylocrebrine (3), the natural products in Group A (Scheme 3). The Suzuki–Miyaura reaction of boronic acids 8a-c with MIDA boronate 9 under anhydrous conditions afforded biphenyl MIDA intermediates 12a-c, which were directly subjected to a second Suzuki–Miyaura reaction with pyridyl bromide 10a under aqueous basic conditions by simply adding H₂O and 10a to the reaction mixture through a slow release technique to produce the desired aza-*ortho*-terphenyl compounds 7a-c.^{9,18} Without complete isolation of 7a-c,¹⁹ they were further subjected to hydrogenation to provide saturated intermediates 13a-c in 62%, 47%, and 24% yields, respectively, over three steps after one column chromatography separation.²⁰

Treatment of compounds 13a-c with methanesulfonyl (Ms) chloride provided dihydroindolizidinium salts 6a-c via activation of the hydroxy group to the corresponding mesylate, followed by a simultaneous intramolecular S_N^2 reaction with a nitrogen atom in the pyridine. Although we attempted to convert dihydroindolizidinium salt 6a to desired product 1 via direct attack of the C-ring to the electrophilic pyridinium ring

Scheme 3. Syntheses of Tylophorine (1), Antofine (2), and Tylocrebrine (3)



(D-ring), no reaction was observed, and **6a** remained unreacted.²¹ Thus, we chose an alternative approach to construct the final B-ring. The pyridinium rings in compounds **6a**-**c** were reduced with NaBH₄, leading to compounds **14a**-**c**, which have a hexahydroindolizine scaffold, in 81%, 86%, and 84% yields, respectively, over two steps. Final oxidative cyclization of the resulting compounds **14a**-**c** in the presence of a vanadium catalyst¹⁵ provided tylophorine (1), antofine (2), and tylocrebrine (3) in 82%, 79%, and 65% yields, respectively.

With this successful result in hand, we further attempted to apply this approach to the syntheses of deoxytylophorine (4) and isotylocrebrine (5), the natural products in group B (Scheme 4). Remarkably, the same synthetic strategy could be applicable to the synthesis of these two natural products with similar efficiency. The one-pot iterative Suzuki-Miyaura coupling reaction of boronic acids, 8b and 8c, with MIDA boronate 9 under anhydrous conditions followed by a second Suzuki-Miyaura reaction of the resulting biphenyl MIDA boronates with pyridyl bromide 10b under slow-release conditions provided the aza-ortho-terphenyl products 7d and 7e. Subsequent alkyne hydrogenation provided 13d and 13e in 45% and 22% yields, respectively, over three steps. Reactions of compounds 13d and 13e with mesyl chloride and subsequent reduction of the pyridinium salts with NaBH₄ afforded hexahydroindolizines, 14d and 14e, in 82% and 87% yields, respectively, over two steps. Vanadium-catalyzed oxidative electrocyclization of 14d and 14e provided deoxytylophorine





(4) and isotylocrebrine (5) in 78% and 58% yields, respectively.

In conclusion, we developed a highly efficient and general building-block-based route for the synthesis of phenanthroindolizidine natural products. The one-pot iterative Suzuki– Miyaura reaction of *ortho*-bromoaryl MIDA boronate with commercially available aryl boronic acids, bearing a suitable methoxy group(s) at the proper position(s), provided the corresponding biphenyl MIDA boronates, and a second Suzuki–Miyaura reaction of a suitable pyridyl bromide, which had a propargyl alcohol at the 2-position, provided the corresponding aza-*ortho*-terphenyl compounds. Subsequent cyclizations of the resulting linear precursors generated five different phenanthroindolizidine natural products. This modular linear-to-cyclized approach should be generally applicable to a range of phenanthroindolizidine alkaloids.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b01397.

Experimental details, characterization data for all the compounds, and copies of NMR spectra (PDF)

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