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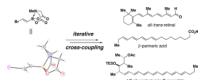
Simple, Efficient, and Modular Syntheses of Polyene Natural Products via Iterative Cross-Coupling

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Abstract

This communication describes the discovery of air-stable and highly versatile B-protected haloalkenylboronic acid building blocks for iterative cross-coupling. These reagents enable the total synthesis of polyene natural products with extraordinary levels of simplicity, efficiency, and modularity. Specifically, all-*trans*-retinal, β -parinaric acid, and one-half the amphotericin B macrolide skeleton were prepared using only the Suzuki-Miyaura reaction in an iterative manner to bring together collections of simple and readily-accessible building blocks. In contrast to their boronic acid counterparts, the intermediate polyenylboronate esters are remarkably stable (to both column purification and storage), which is critical to their successful utilization. Moreover, the reactive boronic acids can be cleanly liberated using very mild aqueous base. These advances have enabled preparation of the longest polyene ever synthesized using the SM reaction. We additionally report, to the best of our knowledge, the first triply metal selective (Zn vs. Sn and B) cross-coupling reaction, the first selective cross-coupling with a differentially-ligated diboron reagent, and the first cross-couplings between polyenylchlorides and vinylboronic acids. Collectively, these new building blocks and methods can dramatically improve the way polyene natural products and their derivatives are synthesized in the laboratory.



Most biologically active small molecules exert their effects via the perturbation of macromolecular targets.¹ There are a few, however, that operate via higher-order mechanisms that lie outside this paradigm. The class of “polyene natural products”² is particularly rich with examples. Perhaps most notable is the antifungal heptaene macrolide amphotericin B (AmB, **1**, Figure 1A), which self-assembles into a membrane-spanning channel complex with functional properties reminiscent of protein-based ion channels.^{3,4} Other polyenes are known to provide structural support for cell membranes,⁵ transduce solar energy into mechanical energy,⁶ serve as pigments for efficient light harvesting⁷ and/or species-specific coloration,⁸ act as fluorescent probes,⁹ and/or quench reactive oxygen species.¹⁰ The existence of these natural prototypes suggests that the potential for small molecules to perform useful functions in living systems likely extends far beyond that which is currently utilized. Unfettered synthetic access to these compounds and their derivatives is paramount for realizing this potential.

The synthesis of polyenes is made challenging by the sensitivity of conjugated double bond frameworks to light, oxygen, and many common synthetic reagents, especially protic and

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Supporting Information Available: Procedures, spectral data, and spectra for all new compounds. X-ray crystallographic data (cif) for **BB1** and **14**. This information is available free of charge via the Internet at <http://pubs.acs.org/>.

Lewis acids. Controlling stereochemistry during the formation of each double bond is also a critical issue. Syntheses based on palladium-mediated cross-coupling are attractive due to the mild, non-acidic, and stereospecific nature of these methods.^{11,12} Among these, the Suzuki-Miyaura (SM) reaction^{11d} stands out due to its use of non-toxic boronic acid reagents and well-precedented functional group compatibility. However, polyenylboronic acids are notoriously unstable,¹³ which precludes their general utilization. We recently developed a simple and flexible strategy for making small molecules involving the iterative cross-coupling of haloboronic acids protected as the corresponding pyramidalized *N*-methyliminodiacetic acid (MIDA, **2**) adducts.¹⁴ We herein report a novel collection of B-protected haloalkenylboronic acid building blocks **BB**₁–**BB**₃ (Fig. 1B) that are strikingly stable to purification and storage, and highly selective towards a wide range of cross-coupling reactions. This stability is maintained in the resulting polyenyl MIDA-boronate ester intermediates, thereby enabling the simple, efficient, and modular construction of a variety of polyene natural products with higher-order functions.

The first targeted building block containing a single double bond (**BB**₁) was prepared via complexation of (*E*)-(2-bromoethenyl)dibromoborane **3**¹⁵ with MIDA (Scheme 1). This reaction was performed on > 20 g scale (75 mmol) to yield the desired bifunctional olefin **BB**₁ as a crystalline, free-flowing solid. X-ray analysis confirmed unambiguously the pyramidalized nature of the boron center.¹⁶ Remarkably, this densely-functionalized alkene is stable to silica gel chromatography and storage for at least 1.5 years on the benchtop under air.

Moreover, **BB**₁ was found to be a very versatile cross-coupling partner (Scheme 1). For example, the sp³-hybridized boronate ester terminus was inert to Buchwald's anhydrous SM conditions¹⁷ thus enabling a selective cross-coupling with (*E*)-styrenylboronic acid **4** to provide dienyl boronate **6** in excellent yield.^{18,19} A Stille coupling between **BB**₁ and vinyl stannane **7** was similarly efficient, yielding butadienyl boronate **8**. Moreover, a Heck coupling with methyl acrylate **9** yielded the unsaturated methyl ester **10** as a single regio- and stereoisomer.

A series of novel *bis*-metallated lynchpin-type reagents¹² were also created. Specifically, Sonogashira coupling between **BB**₁ and TMS-acetylene **11** generated hetero-*bis*-metallated enyne **12**. Although Miyaura borylations²⁰ with (*E*)-1,2-disubstituted vinyl halides are challenging,^{20b} we found that ligand **5a**^{20c} enabled the smooth conversion of **BB**₁ into the novel *bis*-borylated olefin **14** (an X-ray structure of **14** is shown in Scheme 2). Like **BB**₁, **14** is a column- and shelf-stable crystalline solid (stable under air for at least 1.5 years). Finally, Negishi cross-coupling between **BB**₁ and the hetero-*bis*-metallated vinylzinc reagent **15**^{12d} yielded lynchpin **16** in a novel triply-metal selective (Zn vs. Sn and B) reaction.

With the goal of developing robust, shelf-stable building blocks for polyene synthesis, we designed di- and trienyl halides **BB**₂ and **BB**₃ as the corresponding vinyl chlorides.²¹ A direct route to the targeted dienylchloride **BB**₂ was envisioned via a concomitant metal- and halogen-selective SM cross-coupling between *bis*borylated olefin **14** and (*E*)-1-chloro-2-iodoethylene **17**²² (Scheme 2). Due to the absence of a boron p-orbital,^{14a} we hypothesized that the sp³-hybridized MIDA-boronate terminus of **14** would be unreactive relative to the sp²-hybridized pinacol boronic ester. In fact, as shown in Scheme 2, single crystal X-ray diffraction analysis confirmed the distinct hybridization states of the two boron termini of **14**, and a halogen- and boron-selective cross-coupling with **17** yielded the targeted bifunctional diene **BB**₂ as a column- and shelf-stable crystalline solid. This novel type of selective cross-coupling with a differentially-ligated diboron reagent may prove to be generally useful.²³

The final targeted polyene building block containing three double bonds (**BB**₃), was prepared via another metal-¹²ⁱ and halogen-selective cross-coupling between *bis*-functionalized reagents **16** and **17** (Scheme 3). Despite containing a potentially sensitive triene moiety, **BB**₃ is also both column- and shelf-stable.

Although the strength of C–Cl bonds can make the building blocks that contain them quite stable, it also makes these reagents relatively unreactive towards cross-coupling.²⁴ Moreover, the structural and stereochemical liabilities of polyene frameworks preclude the use of forcing conditions. As a result, to the best of our knowledge, SM cross-coupling between a polyenylchloride and a vinylboronic acid has never been previously reported.²⁵ To overcome this challenge, we extensively surveyed a variety of catalysts with different base and solvent combinations for cross-coupling between **BB**₃ and model substrate (*E*)-1-pentenylboronic acid **18**. Ultimately, it was determined that the use of Pd(OAc)₂/phosphine **5b**¹⁷ and Cs₂CO₃ in THF at 45 °C gave good yields of tetraenyl MIDA boronate **19** (Scheme 3).¹⁸

With the three targeted building blocks **BB**₁–**BB**₃ in hand and their potential for selective cross-couplings verified, we explored the utility of these new reagents in the context of total syntheses of polyene natural products that perform higher-order functions. For example, the carotenoid all-*trans*-retinal (**22**) has the ability to transduce solar energy into mechanical energy and is a critical functional component of the light-driven proton pump found in Halobacteria and the photoreception machinery utilized by most animals.⁶ Structure/function studies with this natural product have unique potential to enable the understanding of these phenomena at the molecular level.^{6c}

B-protected haloalkenylboronic acid **BB**₁ was utilized in a highly modular three-step synthesis of retinal from known starting materials (Scheme 4).²⁶ Specifically, the selective SM coupling between **BB**₁ and trienylboronic acid **19**^{26d} yielded the tetraenyl MIDA boronate **20**. Notably, although the instability of **19** precludes its isolation in concentrated form,^{26d} tetraenyl MIDA boronate **20** was isolated via column chromatography as a crystalline solid that can be stored refrigerated for at least one month without decomposition.

A key feature of the MIDA protective group is its capacity for removal under mild, aqueous basic conditions.^{14a} Given the sensitive nature of polyenylboronic acids,¹³ the B-deprotection of intermediate **20** presented a rigorous test for this methodology. In the event, this deprotection proceeded smoothly and subsequent SM coupling of the resulting solution of crude boronic acid with the known β-bromo enal **21**²⁷ succeeded in generating the targeted all-*trans*-retinal **22**.

Another interesting polyene, β-parinaric acid **26**, has been used for more than three decades as a fluorescent probe for membrane properties.^{9,28} In addition, related tetraenoic acids demonstrate remarkable aggregation behaviors²⁹ including the formation of antipodal chiral aggregates from a single enantiomer.^{29b} The utility of **26** and/or its analogs would benefit from more efficient and modular synthetic access to this class of compounds.³⁰

In this vein, the B-protected chlorodienylboronic acid **BB**₂ was employed in a modular, three-step synthesis of β-parinaric acid from readily-available starting materials (Scheme 5). Specifically, using a modification of the newly identified conditions for polyenylchloride cross-coupling, a selective pairing between the bifunctional dienylchloride **BB**₂ and (*E*)-1-butenylboronic acid **23**¹⁶ yielded the column-stable all-*trans* trienyl boronate **24**. B-deprotection of **24** was achieved under mild aqueous basic conditions, and subsequent cross-coupling with vinyl iodide **25**¹⁶ yielded β-parinaric acid **26** as a fluorescent solid.

As a final example, the polyene macrolide AmB³ (Fig. 1A) represents a potential prototype for small molecules that replicate the functions of protein-based ion channels.³¹ An efficient and flexible total synthesis of AmB stands to enable the first systematic dissection of the structure/function relationships that underlie this small molecule-based ion channel activity.⁴

In contrast to strategies based on lynchpin-type reagents,¹² the cross-coupling of B-protected haloboronic acids has the theoretical capacity for limitless iteration.¹⁴ Harnessing this potential, the synthesis of one-half of the AmB macrolide skeleton via recursive SM coupling has been achieved (Scheme 6). Specifically, boronic acid **18** was joined with **BB**₁ to generate dienylylboronate **27**. A subsequent series of B-deprotection and coupling of the resulting dienylylboronic acid with trienylylchloride **BB**₃ yielded column-stable pentaenyl MIDA boronate **28**. Finally, taking advantage of the recent discovery in our laboratories that MIDA boronates can be used directly as surrogates for boronic acids under aqueous SM conditions,³² a one-pot B-deprotection and cross-coupling with dienylylchloride **29**¹⁶ yielded one-half of the amphotericin B skeleton **30**. To the best of our knowledge, this is the longest polyene ever synthesized using the SM reaction. This pathway may ultimately provide the foundation for an efficient and flexible total synthesis of this notoriously challenging natural product.³³

As demonstrated herein, B-protected haloalkenylboronic acid building blocks such as **BB**₁–**BB**₃ have potential for broad utility in the context of total syntheses of polyene natural products. The iterative cross-coupling approach is particularly well-suited for making these types of structures due to the ubiquity of Csp²–Csp² bonds, the mild and stereospecific nature of the coupling methods, and the exceptional stability of the intermediate polyenyl MIDA boronate esters. This simple, efficient, and modular strategy stands to enable the more effective study and widespread utilization of this class of highly functional small molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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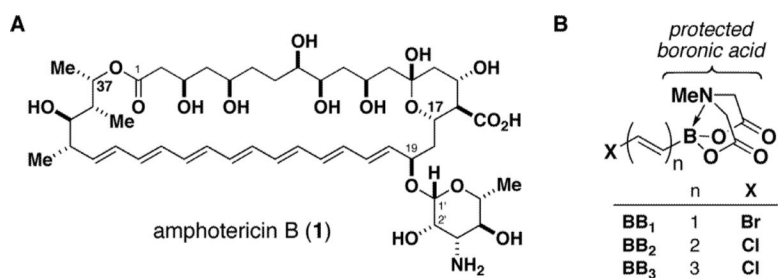
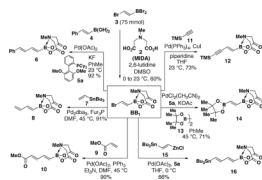
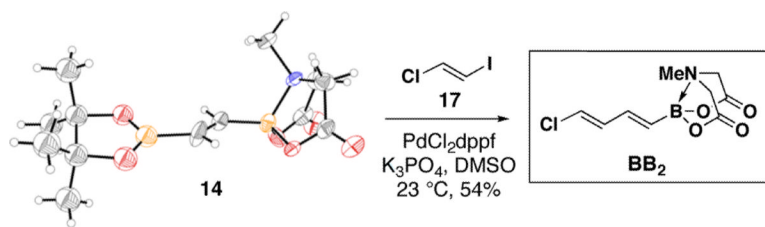


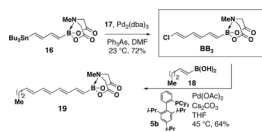
Figure 1.
A. The channel-forming natural product amphotericin B. **B.** A series of B-protected haloalkenylboronic acid building blocks for polyene synthesis.

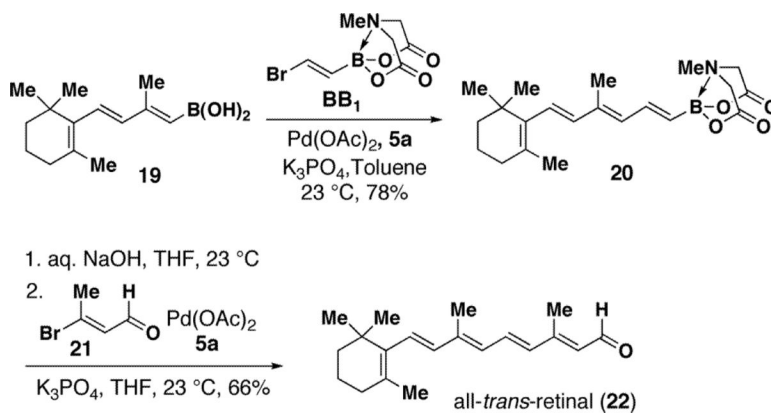


Scheme 1.

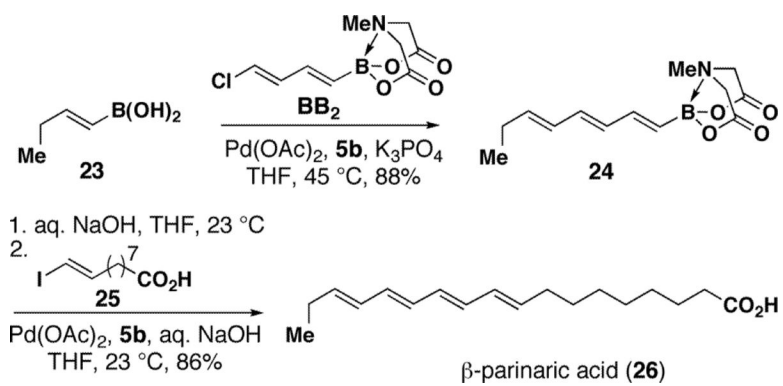


Scheme 2.

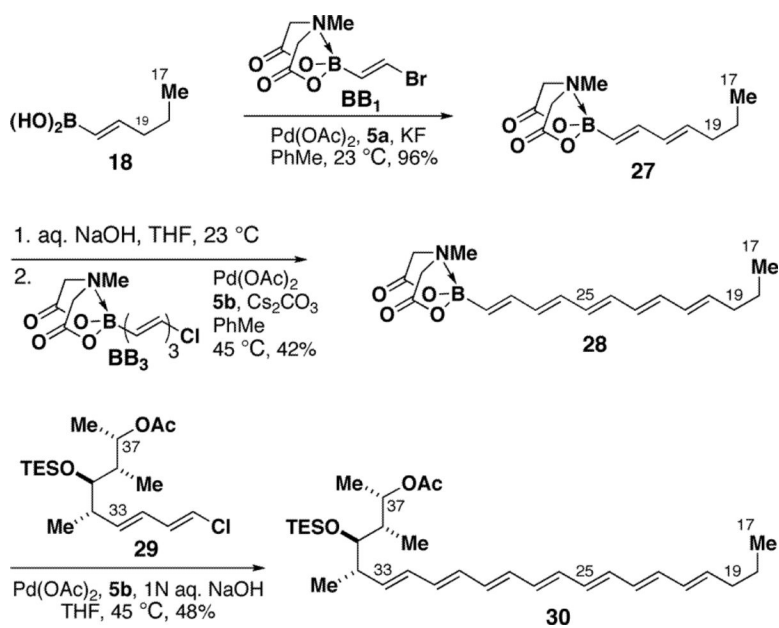
**Scheme 3.**



Scheme 4.



Scheme 5.



Scheme 6.