Aiming to maximally harness the inherent modularity of small molecules, we are pursuing the development of a synthesis strategy based on the iterative cross-coupling (ICC) of bifunctional building blocks representing the substructures that most commonly appear in natural products.[1, 2] In this vein, various combinations of trans- and cis-olefins are found in many small molecules derived from a wide range of biosynthetic pathways, including polyketides, hybrid peptide/polyketides, polyterpines, and fatty acids (Scheme 1).[3, 4]

Enabling stereospecific access to these stereochemically complex polyene frameworks, we herein describe the development of a novel ICC platform that yields bifunctional iodopolyenyl N-methyliminodiacetic acid (MIDA) boronates in all possible stereoisomeric forms. The power of this approach has been realized in the first synthesis of the highly complex (E,E,E,Z,Z,E)-heptaene framework of the ion channel-forming polyene macrolide vacidin A.

We recently reported three haloalkenyl MIDA boronates that enabled the preparation of a subset of polyene motifs by ICC.[2b] Albeit an important step forward, this collection only provided access to all-trans-polyene substructures and utilized polyenylchlorides. Accessing stereochemically complex polyene motifs is substantially more challenging because, in addition to the sensitivities observed with all polyenes to light, oxygen, and acid, frameworks containing cis double bonds can isomerize to the typically more thermodynamically stable all-trans structures. Moreover, poorly reactive polyenylchlorides proved to be minimally effective in complex applications.

To overcome both of these limitations, we pursued a novel strategy for making iodopolyenyl MIDA boronates by ICC of iodide-masked[5] bifunctional building blocks. As shown in Scheme 2A, the approach involves metal-selective cross-coupling of Sn/Ge bis-metalated olefins[6] to generate polyenylgermanium intermediates followed by stereospecific iododegermylations.[7] To the best of our knowledge, iododegermylations of polyenylgermanium species were unreported. However, the facility of halodegermylation[7] vs. halodesilylation[8] of simple olefins suggested that the former process had superior potential to be efficient and stereoretentive in the context of structurally and stereochemically complex polyene systems. Guided by this logic, we hypothesized that iterative cycles of metal-selective cross-coupling of Sn/Ge bis-metatalated olefins[8] to generate polyenygermanium intermediates followed by stereospecific iododegermylations.[7] To the best of our knowledge, iododegermylations of polyenygermanium species were unreported. However, the facility of halodegermylation[7] vs. halodesilylation[8] of simple olefins suggested that the former process had superior potential to be efficient and stereoretentive in the context of structurally and stereochemically complex polyene systems. Guided by this logic, we hypothesized that iterative cycles of metal-selective coupling/iododegermylation with core building blocks 1 and 2 (Scheme 2B) could

**Scheme 1.** Polyene natural products derived from a wide range of biosynthetic pathways.

**Scheme 2.** A) A strategy for ICC of halogen-masked bifunctional building blocks. B) Core building blocks to enable general access to stereoisomeric iodopolyenyl MIDA boronates. C) New iodopolyenyl MIDA boronates for the synthesis of polyene natural products.
provide access to iodopolyenyl MIDA boronates in all possible stereoisomeric forms (Scheme 2 C).

We discovered that (E)-1 and (Z)-1 can both be generated from the novel ethynyl MIDA boronate 6, which in turn can be prepared from readily available Grignard reagent 5.[28,9] Specifically, as shown in Scheme 3, the addition of 5 to the germystannylation of substituted alkynes[15] and the silylstannylation of acetylene,[16] core building block (Z)-1 was efficiently prepared as a single stereoisomer by the palladium-mediated cis-germylstannylation of acetylene gas.

With these four core building blocks in hand, we sought general conditions for efficient cycles of stereospecific metal-selective couplings and iododegermylations (Scheme 2 A). As shown in Scheme 5, we found that Liebeskind-type conditions[17] are remarkably effective for the targeted metal-selective Stille couplings. In fact, using the exact same set of very mild conditions ([Pd(PPh3)4]/CuTC, DMF, 0 °C to 23 °C), all possible combinations of 1 and 2 were stereospecifically coupled in excellent yields to generate dienylgermanium intermediates 8. Completing the envisioned cycle, stereospecific iododegermylations of all four of these intermediates were readily achieved by treatment with I2 in MeOH at −78 °C, thereby providing all of the targeted iododienyl MIDA boronate building blocks 3 in good yields and as single stereoisomers. Harnessing the iterative nature of this strategy, the more advanced trienyl halide (E,E,E)-4 was also readily prepared by simply executing an additional cycle of metal-selective coupling and stereospecific iododegermylation (Scheme 6).

As shown in Table 1, these new bifunctional building blocks collectively enable the preparation of a broad range of stereochemically complex polyyne natural product frameworks. After surveying a variety of catalysts, bases, and solvents we found a very mild set of Buchwald-type[18] cross-coupling conditions [Pd(OAc)2, SPhos or XPhos, Cs2CO3, THF, 23 °C] that proved to be highly effective. Specifically, all possible stereoisomers of 1 and 3 were cross-coupled with both (E)- and (Z)-pentenyl boronic acid 10 in good yields and with outstanding levels of stereoretention.[19] Observations of complete stereoretention even when coupling the sterically encumbered MIDA boronate (Z)-1 (entries 2 and 8) and preparing the very challenging (Z,Z,Z)- triene 22 (entry 10) are particularly notable. Collectively, products 11–22 represent all possible stereoisomers of the core dienyl and trienyl substructures that appear in a wide range of natural products derived from all major biosynthetic

![Diagram](image-url)
Table 1: Stereospecific Suzuki–Miyaura cross-couplings yielding all possible stereoisomers of di- and trienyl MIDA boronates.[a]

| Entry | Boronic acid | Iodoalkenyl MIDA boronate | Product | Yield [%] |
|-------|--------------|---------------------------|---------|-----------|
| 1     | (E)-10       | (E)-1                      |         | 11 95     |
| 2     | (E)-10       | (Z)-1                      |         | 12 77     |
| 3     | (E)-10       | (E,E)-3                    |         | 13 75     |
| 4     | (E)-10       | (E,Z)-3                    |         | 14 78     |
| 5     | (E)-10       | (Z,E)-3                    |         | 15 87     |
| 6     | (E)-10       | (Z,Z)-3                    |         | 16 64     |
| 7     | (Z)-10       | (E)-1                      |         | 17 91     |
| 8     | (Z)-10       | (E,E)-3                    |         | 18 74     |
| 9     | (Z)-10       | (E,Z)-3                    |         | 19 77     |
| 10    | (Z)-10       | (E,Z)-3                    |         | 20 84     |
| 11    | (Z)-10       | (Z,E)-3                    |         | 21 82     |
| 12    | (Z)-10       | (Z,Z)-3                    |         | 22 62     |

[a] 1.0 equiv 1 or 3, 1.5 equiv 10, Pd(OAc)$_2$, SPhos (entries 1, 3, 4, 7, 9, 10) or XPhos (entries 2, 5, 6, 8, 11, 12), Cs$_2$CO$_3$, THF, 23°C.

As a final test for this new platform, we targeted an ICC-based synthesis of the stereochemically complex polyene core of the exceptionally potent ion channel forming natural product vacidin A (Scheme 1). Interestingly, and in contrast to almost all other known polyene macrolide antibiotics, vacidin A contains two cis double bonds embedded within an otherwise all-trans heptaene framework. As shown in Scheme 7, hydrolysis of cross-coupling product 13 (Table 1, entry 3) with aqueous base followed by coupling of the resulting (E,E,E)-trienylboronic acid to iododienyl MIDA boronate (Z,Z)-3 under anhydrous conditions yielded the desired (Z,Z,E,E,E)-pentae 23. Avoiding the need to isolate the corresponding highly unstable boronic acid, a final one-pot MIDA hydrolysis and cross-coupling with dienyl iodide 24 completed the first synthesis of the vacidin A (E,E,E,Z,Z,E,E)-heptaene framework 25. Demonstrating the powerful simplicity of the ICC approach, this highly complex polyene motif was generated using only a single reaction to unite a collection of building blocks in which all of the required stereoisomeric relationships were pre-installed.

The metal-selective coupling/iodododegermylation strategy described herein provides access to a wide range of useful building blocks for the synthesis of complex polyene motifs. Overcoming previous limitations, this platform enables stereospecific preparation of polyenes in all possible stereoisomeric forms. These new building blocks represent important additions to a growing collection of MIDA boronates designed to support the development of a simple and flexible platform for the efficient synthesis of small molecules by ICC.[21]
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Generally, no alternative stereoisomers were observed by NMR spectroscopy of the crude products. Polyene 20 partially isomerized upon concentration (see Supporting Information).

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The indicated configuration of the polyene motif in 25 is consistent with an extensive series of multidimensional NMR studies (see Supporting Information for details).