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Stereoretentive Suzuki−Miyaura Coupling of Haloallenes Enables Fully Stereocontrolled Access to (−)-Peridinin

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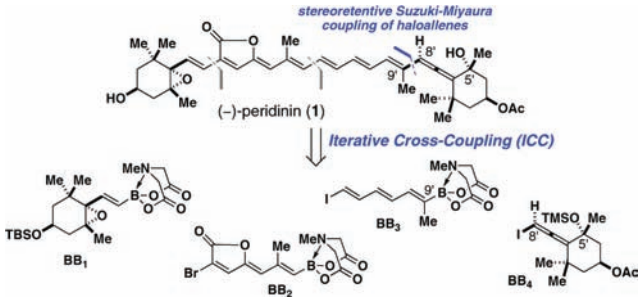
Deficiencies of antilipoperoxidant proteins have been associated with atherosclerosis, rheumatoid arthritis, and cancer and may contribute to an accelerated aging process.[1] Small molecules with the capacity to replicate the functions of these proteins could therefore have a major positive impact on human health. In contrast to most carotenoids,[2] the C37-norcarotenoid peridinin (**1**)[3] may exert antilipoperoxidant activities primarily through self-preserving mechanisms, including catalytic quenching of $^1O_2$ and decreasing membrane permeability to other reactive oxygen species.[4] Isolation from natural sources is very inefficient,[3b] however, and the sensitive and stereogenic allene moiety central to the structure of **1** has made its stereoselective synthesis very challenging.[5,6] As a result, the underpinnings of these activities have been only minimally explored.[4,7] To facilitate systematic studies of such small molecules with protein-like functions, we recently introduced a simple, efficient, and flexible synthesis strategy that involves the iterative cross-coupling (ICC) of bifunctional haloboronic acids masked as the corresponding *N*-methyliminodiacetic acid (MIDA) boronates.[8] Enabled by this ICC approach and the development of new methodology for the highly stereoretentive Suzuki−Miyaura (SM) cross-coupling of haloallenes, we herein report the first fully stereocontrolled total synthesis of (−)-**1**.

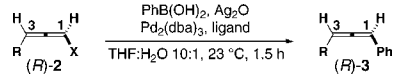
Scheme 1



Guided by the ICC strategy,[8] we applied only SM transforms to retrosynthesize **1** into four building blocks, **BB$_1$**−**BB$_4$**, having all of the required functionality preinstalled in the correct oxidation states and with the desired stereochemical relationships (Scheme 1). We recognized, however, that the disconnection between C8′/C9′ corresponded to a stereoretentive SM coupling with a haloallene. Albeit potentially very useful in the preparation of many natural products,[9] this was an unprecedented transformation[10] that first required development.

In related Negishi couplings,[11] chloro- and bromoallenes yield products representing net stereochemical inversion, whereas the corresponding iodoallenes tend to favor stereoretention. These results were attributed to two competing mechanisms involving direct oxidative addition (OA) at C−X or indirect S_N2'-like OA[12] followed by a suprafacial 1,3 shift of Pd.[13] Attempts to form the C8′/C9′ bond in **1** via a Stille coupling have been complicated by similar issues.[6] Consistent with these precedents, using conditions similar to those reported to promote the SM coupling of achiral haloallenes,[10a] the reaction of PhB(OH)$_2$ with enantioenriched chloro- and bromoallenes (*R*)-**2a**,**b** demonstrated net stereoinversion to provide (*S*)-**3a** as the major product (Table 1, entries 1−2). In contrast, coupling of iodoallene (*R*)-**2c** yielded (*R*)-**3a** with a moderate 72% stereoretention (entry 3).

Table 1. Development of the First Stereocontrolled SM Coupling of Chiral Haloallenes



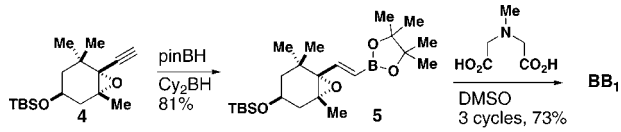
entry	2	R	X	ligand	3	% stereoretention[a,b]
1	(*R*)-**2a**	*t*-Bu	Cl	PPh_3	(*S*)-**3a**	−78
2	(*R*)-**2b**	*t*-Bu	Br	PPh_3	(*S*)-**3a**	−78
3	(*R*)-**2c**	*t*-Bu	I	PPh_3	(*R*)-**3a**	72
4	(*R*)-**2d**	3-pentyl	I	PPh_3	(*R*)-**3b**	58
5	(*R*)-**2e**	*n*-pentyl	I	PPh_3	(*R*)-**3c**	25
6	(*R*)-**2c**	*t*-Bu	I	$PFur_3$	(*R*)-**3a**	80
7	(*R*)-**2c**	*t*-Bu	I	PCy_3	(*R*)-**3a**	50
8	(*R*)-**2c**	*t*-Bu	I	P*t*-Bu_2Me	(*R*)-**3a**	71
9	(*R*)-**2c**	*t*-Bu	I	P*o*-Tol_3	(*R*)-**3a**	91
10	(*R*)-**2c**	*t*-Bu	I	P*t*-Bu_3	(*R*)-**3a**	93
11	(*R*)-**2c**	*t*-Bu	I	XPhos	(*R*)-**3a**	91
12[c]	(*R*)-**2c**	*t*-Bu	I	XPhos	(*R*)-**3a**	>99[d]
13[c]	(*R*)-**2d**	3-pentyl	I	XPhos	(*R*)-**3b**	>99
14[c]	(*R*)-**2e**	*n*-pentyl	I	XPhos	(*R*)-**3c**	85

[a] % stereoretention = ee product/ee starting material (chiral GC, average of 2 runs); negative values reflect net stereoinversion. [b] Unoptimized GC yields ranged from 10 to 83%. [c] Hexane:THF:H_2O 9:1:1 was used as solvent. [d] Isolated yield = 61%.

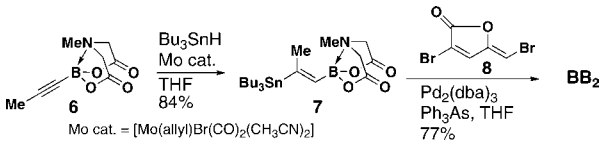
Building on this starting point, we tested the previously unconfirmed hypothesis[11] that maximized steric bulk at C3 of a haloallene could promote stereoretention, presumably by disfavoring S_N2'-like OA. Specifically, we evaluated a series of substrates **2c**−**e** having progressively smaller R groups at C3 and indeed observed decreased stereoretention (entries 3−5). Guided by reciprocal logic,[14] we hypothesized that bulky phosphine ligands[15] would also promote stereoretentive direct OA at the less sterically hindered C1. In fact, in contrast to smaller ligands (entries 3, 6−8), >90% stereoretention was observed for phosphine ligands having cone angles >180° (entries 9−11).[16] With air-stable XPhos,[15a] optimization of solvent led to >99% stereoretention and 61% isolated yield (entry 12). Substantial improvements in stereoretention were also observed for couplings with **2d** and **2e** under these optimized conditions (entries 13 and 14).

Collectively, these findings revealed that maximized stereoretention in the SM coupling of chiral haloallenes can best be achieved using allenyl iodide substrates having steric bulk at C3 in combination with sterically bulky phosphine ligands. Guided by these

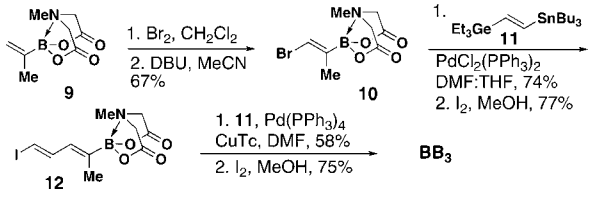
Scheme 2



Scheme 3



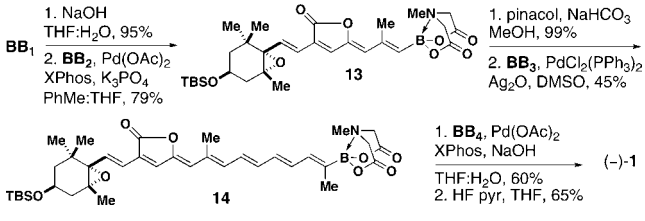
Scheme 4



general principles, we designed $\mathbf{BB_4}$[6b] for peridinin (Scheme 1) to include both an allenyl iodide and a sterically bulky, yet still easily removable, TMS ether at C5′.

Preparation of the remaining building blocks was enabled by some highly favorable features of the MIDA boronate platform.[8] Specifically, following a hydroboration of alkyne **4**[5b] to give pinacol ester **5**, a direct transesterification to form the air-stable MIDA boronate $\mathbf{BB_1}$ was achieved (Scheme 2).[17] This direct transesterification from a boronic ester to a MIDA boronate avoids the intermediacy of unstable boronic acids. The unique compatibilities of the MIDA boronate functional group with a wide range of reaction conditions[8c] and chromatography[8] were utilized to prepare the final two building blocks. Specifically, propynyl MIDA boronate **6** (Supporting Information) underwent highly regio- and stereocontrolled molybdenum-catalyzed hydrostannylation[18] to yield bis-metalated olefin **7** (Scheme 3). A subsequent metal and halide selective coupling between **7** and lactone **8**[19] provided $\mathbf{BB_2}$ as a single stereoisomer.[20] The final building block $\mathbf{BB_3}$ was prepared via initial bromination of commercially available **9** followed by regio- and stereoselective elimination to generate the novel trisubstituted bromoalkenyl MIDA boronate **10** as a single stereoisomer[20] (Scheme 4). Two cycles of our recently developed methodology[8e] for stereospecific metal-selective cross-coupling with bis-metalated olefin **11**[21] followed by stereoretentive iododegermylation[22] provided $\mathbf{BB_3}$.

Scheme 5



The synthesis of **1** was completed using only iterative SM couplings to assemble these four building blocks, thereby completely avoiding mixtures of olefin isomers[5,6] (Scheme 5). Hydrolysis of $\mathbf{BB_1}$ followed by B-selective cross-coupling with $\mathbf{BB_2}$ provided tetraenyl MIDA boronate **13**. The corresponding boronic acid proved to be unstable; thus a new tactic was developed to promote the next cycle of B-activation and coupling. Specifically, in a novel transformation, **13** was directly converted into the corresponding pinacol ester, which was an effective intermediate for B-selective coupling with $\mathbf{BB_3}$. The resulting highly complex heptaenyl MIDA boronate **14** was stable to chromatography and storage. Conversely, attempts to isolate the heptaenyl boronic acid derived from **14** or to utilize the corresponding pinacol ester were not fruitful. To solve this challenging problem, we hybridized the principles established above for allenyl halide coupling (Table 1) with in situ release of the unstable boronic acid[8d,b] derived from MIDA boronate **14** to promote the final union with $\mathbf{BB_4}$ in good yield *and with complete stereoretention*. Global desilylation concluded, to the best of our knowledge, the first completely stereocontrolled total synthesis of (−)-peridinin.

This efficient and highly modular pathway to **1** stands to facilitate systematic dissection of the structure/function relationships that underlie the self-preserving antilipoperoxidant activities of this small molecule natural product.

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Supporting Information Available: Procedures, complete ref 1a, and spectral and crystallographic data (.cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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