Stereoretentive Suzuki–Miyaura Coupling of Haloallenes Enables the Total Synthesis of (–)-Peridinin

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Lipid peroxidation can have a substantial negative impact on the quality of human health. The oxidative degradation of lipid membranes has been correlated with occurrences of cancer, heart disease, stroke, age related macular degeneration, and many other diseases. Evidence suggests that carotenoids can limit the peroxidation of lipids, and, in particular, peridinin has demonstrated potent anticancer and antioxidant activity. In contrast to most carotenoids, the C37-norcarotenoid peridinin may exert antilipoperoxidant activities primarily through self-preserving mechanisms, including catalytic quenching of $^1O_2$ and decreasing membrane permeability to other reactive oxygen species. Attempts to study these mechanisms have been impeded by the cumbersome procedures required to isolate the quantities of peridinin needed to methodically probe the carotenoid/membrane/oxidant interactions. In contrast to these isolation protocols, synthetic organic chemistry can, in theory, provide ready access to both peridinin and its key derivatives. However, the complex polyene core and the stereogenic allene moiety central to the structure of peridinin have made its stereoselective synthesis very challenging. Enabled by the iterative cross-coupling approach for the synthesis of small molecules and the development of new methodology for the highly stereoretentive Suzuki-Miyaura cross-coupling of haloallenes, we herein report the first fully stereocontrolled total synthesis of peridinin. Moreover, the efficient and highly modular nature of this synthesis promises to enable systematic dissection of the structure/function relationships that underlie the self-preserving antilipoperoxidant activities of peridinin.