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The Stille Reaction in the Synthesis of Carotenoid Butenolides: Synthesis of 6′-*epi*-Peridinin

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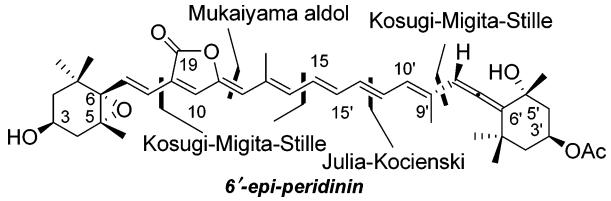
ABSTRACT



A new strategy for carotenoid butenolides has been developed that is based in part in halogen-selective Stille cross-coupling of dihalogenated ylidenebutenolide segment 2 and highly functionalized alkenylstannanes.

Metal-catalyzed cross-coupling reactions have revolutionized retrosynthetic planning, making C−C single bond disconnections one of the methods of choice for the reliable control of olefin geometries in conjugated dienes and short polyenes.[1] The construction of the carotenoid skeleton has traditionally been the battleground for testing the performance of polyene-forming processes, due to the configurational instability and chemical sensitivity of these natural products to a variety of reaction conditions.[2] Double bond-formation strategies, such as the Wittig reaction or the Julia-Lythgoe olefination, performed in consecutive or convergent fashion, have proven efficient in the preparation of carotenoids, even at the industrial scale. The alternative strategy, featuring generation of single bonds connecting Csp^2 atoms, is a more recent development. Negishi described the Pd- and Zn-catalyzed cross-coupling of alkenyl fragments to afford β,β-carotene and other all-carbon (apo)carotenoids.[3] Our group reported the synthesis of β,β-carotene and (3*R*,3′*R*)-zeaxanthin by a convergent two-directional Stille cross-coupling.[4] The approach, however, also took advantage of the symmetry of the carotenoids, and manipulation of these unstable polyenes was minimized. As an extension of this work, and in order to fully reveal the performance of the metal-catalyzed cross-coupling processes in this field, we embarked on a program aimed at the preparation of nonsymmetrical, highly functionalized carotenoids.

Peridinin **1** is a carotenoid butenolide isolated from planktonic algae dinoflagelates,[5] which are deemed responsible for "red tide" episodes. The sophisticated and highly efficient light-harvesting device of dinoflagelates is assembled from noncovalent arrangements of chlorophyll and peridinin embebbed in a protein scaffold.[6] Relative to common C40-carotenoids, peridinin **1** is a C37-dicyclic norcarotenoid[7] containing, in addition to the γ-alkylidenebutenolide ring structure, an abnormal arrangement of methyl

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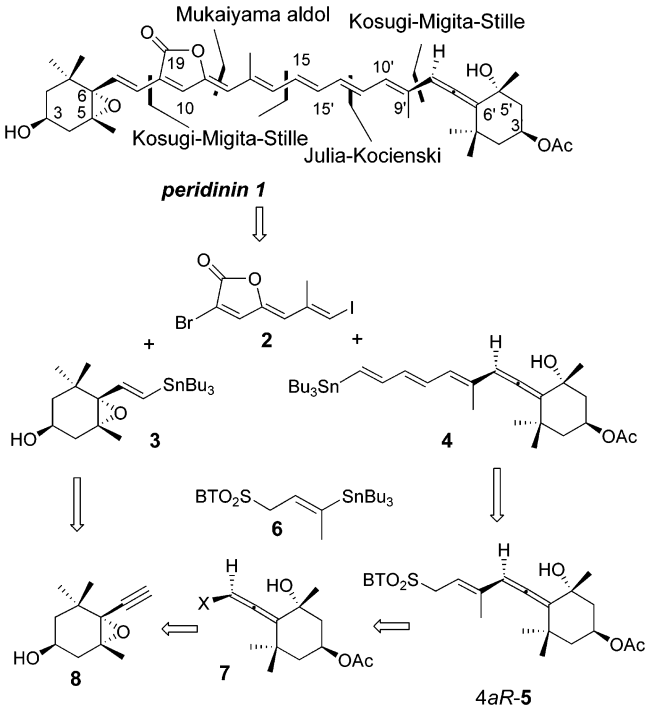
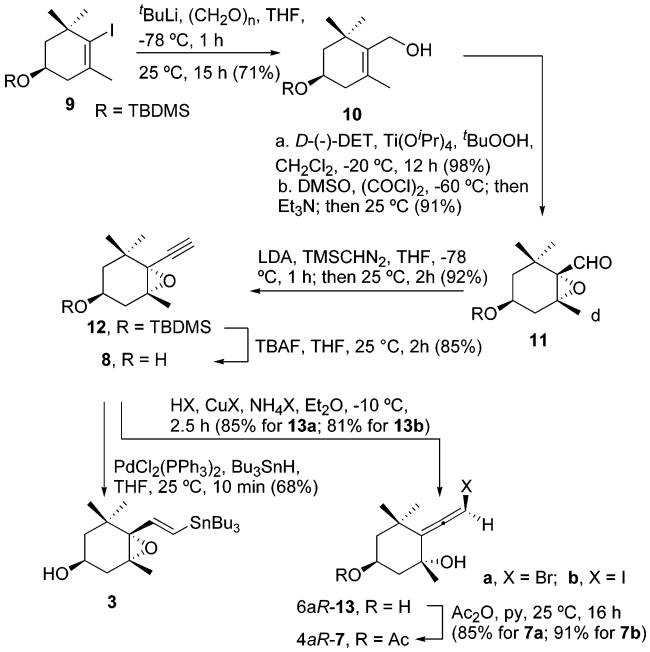


Figure 1.

groups, five chiral centers and a chiral allene axis. Our retrosynthetic analysis of peridinin is shown in Figure 1.

We envisioned the synthesis of **1** by convergent Stille cross-coupling reactions[8] of a central γ-alkylidenebutenolide unit[9] **2**,[10] containing halogens of modulated reactivity,[11] and functionalized alkenylstannanes **3** and **4**. The latter could, in turn, be prepared by a modified-Julia reaction[12] of β-stannylacrolein and γ-allenyl allyl benzothiazolyl sulfone **5**. We anticipated that **5** would be formed by yet another Stille cross-coupling of stannyl sulfone **6** and haloallene **7**. Enantiopure alkynyl oxirane **8**, accessible by a Sharpless asymmetric epoxidation (SAE) of an appropriate precursor, was identified as the common ultimate building block to access both **3** and **4**. On implementation of this scheme, we found either a nonstereoselective outcome or a complete inversion of configuration of the chiral axis in the Stille cross-coupling of **6** and **7**. Despite this shortcoming, the synthetic approach to 6′-*epi*-peridinin by position-selective and stereoselective Stille coupling reactions of dihalogenated γ-alkylidenebutenolide **2** complements the two previous syntheses of natural peridinin **1** reported by Ito[13] and Katsumura.[14]

Scheme 1



The synthesis of the chiral cyclic end groups is shown in Scheme 1. Previously described[4] alkenyliodide **9** was converted into allyl alcohol **10** by iodine−lithium exchange (*t*-BuLi, THF, −78 °C) followed by trapping with paraformaldehyde (71%). Excellent yield (98%) and enantioselectivity (>98% ee, as shown by chiral HPLC of 6*aR*-**13**) in the SAE[15] of **10** were obtained only when stoichiometric quantities of $Ti(O^iPr)_4$ and (−)-DET were employed (CH_2Cl_2, −20 °C, 12 h) in order to reduce the deleterious effects of extended reaction times (36 h) required in the substoichiometric version. Swern oxidation[16] of the epoxy alcohol to give **11**[14] (91%) was followed by Colvin rearrangement[17] induced upon treatment with the anion of trimethylsilyldiazomethane affording alkynyl oxirane **12** in 92% yield.

Palladium-catalyzed hydrostannylation[18] [$PdCl_2(PPh_3)_2$, Bu_3SnH, THF, 25 °C, 10 min, 68%] was most effective on deprotected alkyne **8**[14] (TBAF, THF, 85%), affording enantiopure alkenylstannane **3**, which was purified by reversed-phase chromatography. Likewise, opening of alkynyl oxirane **8** under the conditions of Chemla[19] (48% HBr, CuBr, NH_4Br, Et_2O, −10 °C, 2.5 h; or 57% HI, CuI, NH_4I, Et_2O,

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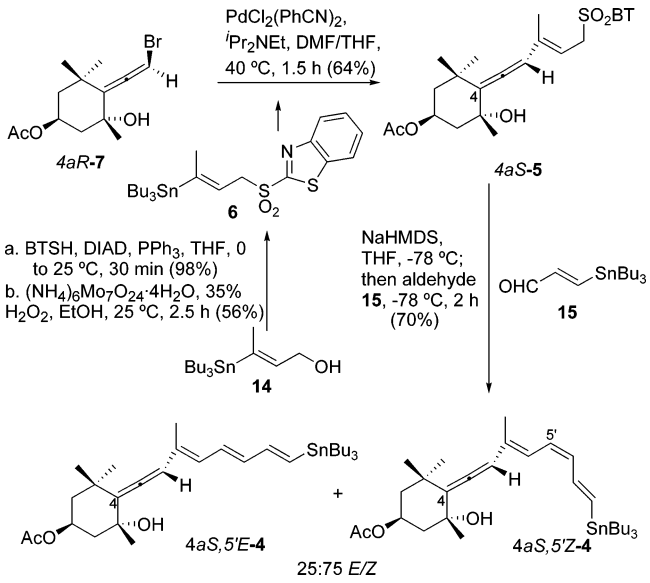
−10 °C, 2.5 h) took place regio- and stereoselectively and provided haloallene **13**, the product of S_N2' displacement exclusively (85% yield for **13a**; 81% for **13b**).

Efficient acetylation of haloallene **13** required treatment with acetic anhydride and pyridine at room temperature in order to minimize epimerization of the chiral axis. Allene 4*aR*-**7a** was acquired in 85% yield admixed with the 4*aS* diastereomer (>20:1) whereas the yield of 4*aR*-**7b** was 91% (11:1 ratio). The diastereomers were separated and the structure of 4*aR*-**7a** was secured by X-ray diffraction.[20]

On the other hand, stannylcupration of but-2-yn-1-ol[21] provided alkenylstannane **14** (Scheme 2). This compound

Scheme 2



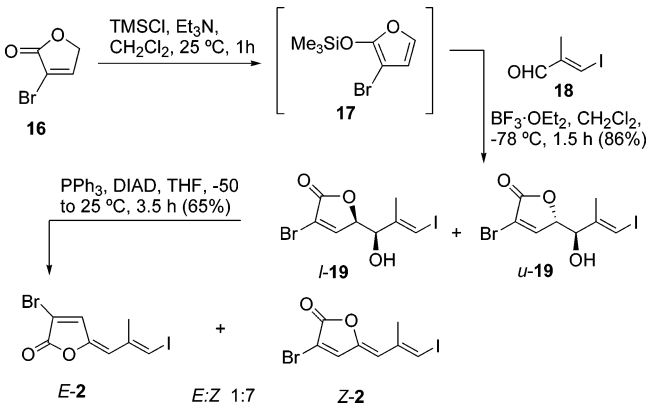
was transformed into benzothiazolyl allyl sulfone **6** using the Mitsunobu variant (BTSH, PPh_3, DIAD, THF, 0 to 25 °C, 98%)[22] followed by oxidation[23] of the sulfide with a peroxymolybdate(VI) reagent[24] [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 35% H_2O_2, EtOH, 25 °C, 56%].

No precedents on the Stille cross-coupling reaction of chiral enantiopure haloallenes[25] with alkenylstannanes existed prior to this work. The stereochemical outcome of the related palladium-catalyzed cross-coupling reactions of enantiopure halogenated allenes with organozinc reagents was reported by Vermeer[26] to be halogen-dependent (Br: inversion; I: retention). Despite extensive experimentation, varying the palladium catalysts [$Pd_2(dba)_3$/$AsPh_3$, $PdCl_2(PhCN)_2$, $Pd_2(dba)_3$/P^tBu_3, $Pd_2(dba)_3$/2-(di-*tert*-butylphosphino)biphenyl], solvent (DMF/THF, NMP, dioxane), temperature (25−80 °C), and additives (amine base) we were unable to induce direct cross-coupling selectively by oxidative addition of Pd(0) to the haloallenes 4*aR*-**7**. In the most favorable case, inseparable allenyl allyl sulfones 4*aS*-**5** and its epimer 4*aR*-**5** were obtained in a 2:1 ratio when the iodoallene 4*aR*-**7b** and stannane **6** were treated with $Pd_2(dba)_3$ and the bulky 2-(di-*tert*-butylphosphino)biphenyl at 25 °C. Sulfone 4*aS*-**5** was, however, obtained as a single product in most coupling trials involving **6** and bromoallene 4*aR*-**7a**, most efficiently (64%) under the catalysis of $PdCl_2(PhCN)_2$ in THF/DMF in the presence of Hünig's base at 40 °C. The structure of 4*aS*-**5** was confirmed by X-ray diffraction.[20] The allene axis inversion was interpreted as resulting from an *anti*-selective S_N2'-displacement of bromide by palladium followed by [1,3]-sigmatropic shift of propargyl- to allenylpalladium[25a,26c] before transmetalation and progression through the catalytic cycle.[27]

Modified−Julia condensation[12] of 4*aS*-**5** and 3-(tributylstannyl)acrolein **15** (NaHDMS, THF, −78 to +25 °C) afforded a mixture of allenyl trienylstannanes 4*aS*-**4** in a 3:1 ratio and 70% yield. Separation allowed the characterization of the major isomer as 5′*Z*-**4**,[28] as shown by analysis of proton coupling constants and NOE difference experiments. The minor isomer, presumably all-*E*-**4**, could not be characterized due to extensive degradation.

Preparation of the central dihalogenated C8-unit was based on the vinylogous Mukaiyama condensation of 3-bromo-2-trimethylsiloxyfuran **17**[10] and 3-iodo-methacrolein **18**[29] at −90 °C under catalysis of $BF_3\cdot OEt_2$,[30,10] which provided in 86% yield a mixture of the *syn* and *anti* aldol diastereomers **19**[10] in a 10:1 ratio, as confirmed by X-ray analysis of the major component (Scheme 3).[20] The major product *l*-**19**

Scheme 3



(78%) was converted through β-elimination with excess PPh_3/DEAD[30,10] into the desired halogen-differentiated alkylidenebutenolide **2**, a separable 7:1 mixture of *Z*/*E* isomers (65%).

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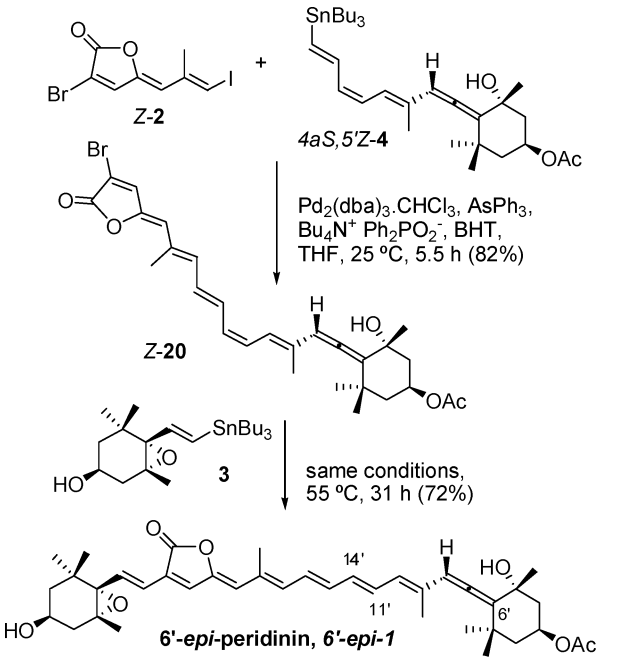
With all fragments at hand, the stage was now set for the crucial Stille cross-coupling reactions. 2-Bromo-γ-alkylidenebutenolides have been coupled to simple alkenyl stannanes using the catalytic combination of $Pd_2(dba)_3{\cdot}CHCl_3$ and $AsPh_3$.[31] Stannane 4*aS*,5′*Z* -**4** proved to be less reactive, and required stirring with *Z*-**2** at ambient temperature for 18 h under the described conditions in order to reach completion (Scheme 4). The extended reaction times proved however

Scheme 4



detrimental to the stereochemical integrity of the polyenes. Fortunately, the beneficial effect of tetrabutylammonium phosphinate[32] Bu_4N^+ $Ph_2PO_2^-$ allowed reduction of the reaction time to 5.5 h. The optimized 82% yield of polyene **20** (5:1 isomer ratio) was obtained when BHT was added, and the mixture was carefully deoxygenated. The major product was shown to be *Z*-**20** through analysis of the ^1H NMR coupling constants and NOE difference experiments, confirming retention of configuration in the coupling partners. The structure of the highly unstable minor isomer was assumed to be *E*-**20**, a first indication of the sensitivity of the polyene geometry to the action of palladium catalysis. For completion of the synthesis, coupling of *Z*-**20** and the reluctant alkenylstannane **3** required heating to 55 °C for 31 h under the same reaction conditions optimized above [$Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, Bu_4N^+ $Ph_2PO_2^-$, BHT, THF]. After chromatography, a single product was obtained in 72% yield. Its structure was assigned as 6′-*epi*-peridinin (6′-*epi*-**1**) by rigorous analysis of coupling constants and 2D-HMQC-TOCSY experiments (750 MHz). In addition to the stereoselective coupling reaction, palladium also induced isomerization[33] of the 11′*Z*-olefin (peridinin numbering) to the most stable *E* isomer, 6′-*epi*-**1**. This compound has been previously obtained by iodine-assisted photoisomerization of natural peridinin after tedious separation of up to eight stereoisomers.[34]

In summary, the epimer at the allene chiral axis of the carotenoid butenolide peridinin has been synthesized using a convergent approach featuring stereoselective Stille reactions. The modified Julia coupling affords a *Z*-configured allenyl trienylstannane, but it is fortunate that this isomer is stable to proceed toward the final polyene, being isomerized in the last Stille coupling of the sequence, presumably by the action of palladium. Although the chiral axis of natural peridinin is easily obtained by DIBAL reduction of alkynyl oxiranes,[13,14] our efforts are instead directed toward developing reaction conditions ensuring retention of configuration in the Stille coupling of haloallenes in order to have access to configurationally distinct building blocks and further extend the palladium-catalyzed cross-coupling strategy to the preparation of a large set of analogues for studies of artificial supramolecular photosynthetic devices.

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Supporting Information Available: Typical experimental procedures for the synthesis of all compounds, and their physical and spectroscopic data, as well as X-ray structural data of compounds 4*aR*-**7**, 4*aS*-**5**, and *lk*-**19** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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