Syntheses of ylidenbutenolide-modified derivatives of peridinin and their stereochemical and spectral characteristics†

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Peridinin is a light-harvesting carotenoid found in oceanic photosynthetic organisms. It possesses a unique γ-ylidenbutenolide function and engages in energy transfer to chlorophyll a with very high (>90%) efficiency. In order to examine the relationship between the unique structure of peridinin and its facility in carrying out energy transfer, we have synthesized two different ylidenbutenolide-modified derivatives of peridinin. In this communication, the details of the syntheses are described as are the stereochemical and spectral characteristics of the derivatives; the novel ylidenbutenolide functional group stabilizes the molecule and maintains the conjugated π-electron system in an all-*trans* configuration.

Peridinin (Fig. 1) is found along with chlorophyll a (Chl a) in a water-soluble light-harvesting complex of dinoflagellates known as the peridinin-Chl a-protein (PCP).[1] In this complex, peridinin exhibits an exceptionally high efficiency of energy transfer to Chl a.[2] Because peridinin possesses both an allene function and a unique γ-ylidenbutenolide group in addition to its C37 carbon skeleton, the question arises what is the relationship between these functional groups and the ability of peridinin to achieve such a high level of energy transfer? Using a highly efficient method for peridinin synthesis previously reported by us,[3] we have carried out the synthesis of a series of allene-modified[4] and π-electron chain length-modified[5] derivatives of peridinin. Ultrafast time-resolved optical absorption and Stark spectroscopic measurements performed on these peridinin-modified derivatives revealed that an intramolecular charge transfer (ICT) state exists as a separate electronic state from the S_1 state,[6] and that the allene and C37 carbon skeleton contribute to the generation of a large dipole moment in the excited state of the molecule.[4,5] In this work we now turn our attention to the role of the γ-ylidenbutenolide functional group in controlling the spectroscopic and spectral properties of peridinin.

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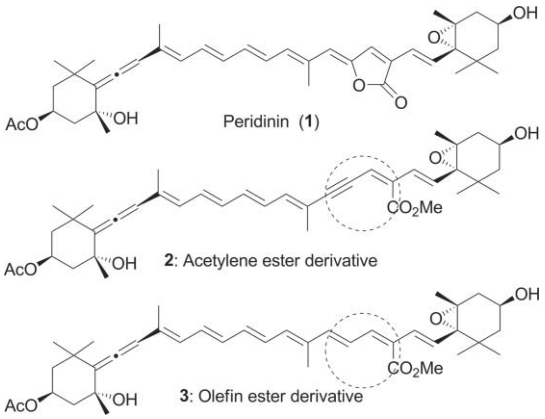


Fig. 1 Peridinin (**1**) and ylidenbutenolide-modified derivatives **2** and **3**.

Previously, we reported the synthesis of peridinin (**1**) by a coupling of the allenic half-segment **4** and the ylidenbutenolide half-segment **5** (Fig. 2).[3] According to our stereocontrolled syntheses of peridinin and derivatives,[4,5] we planned to synthesize acetylene ester derivative **2** and olefin ester derivative **3** by a coupling between the allenic half-segment **4** and the corresponding ylidenbutenolide-modified half-segments **6** and **7** using the modified Julia olefination reaction. Both half-segments can be synthesized from the optically homogenous epoxyaldehyde derivative **8**, which can be prepared from (–)-actinol.[7]

First, the synthesis of acetylene ester derivative **2** is described. The stereocontrolled synthesis of half-segment **6** is shown in Scheme 1. Butenolide **9** prepared from (–)-epoxyaldehyde **8** by the reported procedure,[3] was treated with diisopropylethylamine and methyl iodide in DMSO produced the desired aldehyde **10** resulting from the stereocontrolled ring opening of γ-hydroxybutenolide in **9**. The obtained aldehyde **10** was transformed into **12** by the Corey–Fuchs' procedure followed by a TBAF treatment.[3] Sonogashira cross-coupling[8] between **12** and **13** in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI in THF produced the desired alcohol in 66% yield, which was transformed into the acetylene ester segment **6** by MnO_2 oxidation. The all-*trans* structure depicted as **6** was confirmed by ^1H NMR spectroscopic analysis. Meanwhile, allenic segment **4** was synthesized as previously described.[3]

With allenic segment **4** and acetylene ester segment **6** in hand, the modified Julia olefination[9] was explored as the final step for the synthesis of the acetylene ester derivative **2**. The reaction of an anion derived from **4** with **6** at –78 °C proceeded smoothly within 5 min in the dark to produce the desired compound **2** in 63% amount as a mixture of stereoisomers (Scheme 2). Generally, the

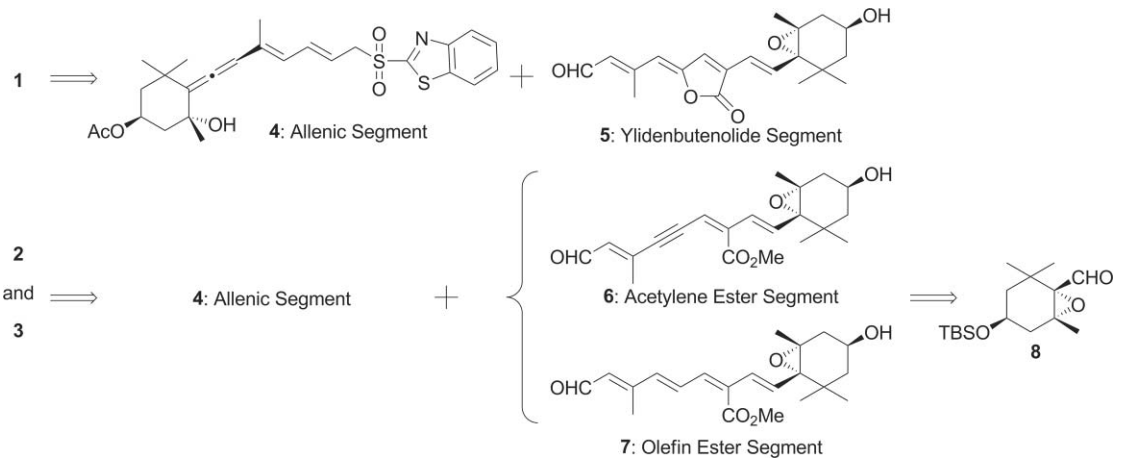
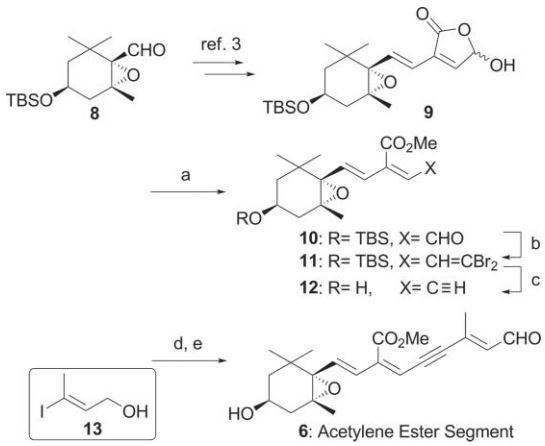
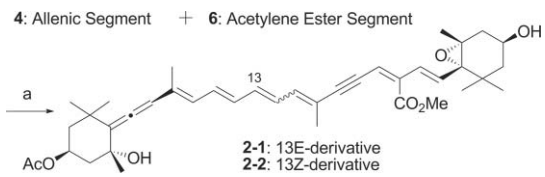


Fig. 2 Synthetic strategy.



Scheme 1 Synthesis of acetylene ester segment **6**. *Reagents and conditions*: (a) $^{i}Pr_2NEt$, MeI, DMSO, r.t., 15 min; (b) CBr_4, PPh_3, Et_3N, CH_2Cl_2, –20 °C to –60 °C, 5 min, 76% for 2 steps; (c) TBAF, THF, 55 °C, 2 h, 41%; (d) **13**, $Pd(PPh_3)_4$, CuI, Et_3N, THF, r.t., 40 min, 66%; (e) MnO_2, Et_2O, r.t., 5 min.



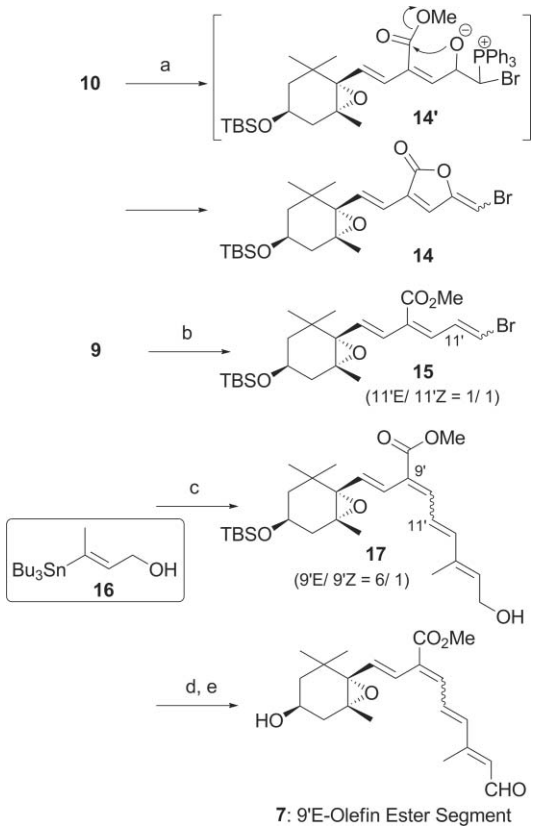
Scheme 2 Synthesis of acetylene ester derivative **2**. *Reagents and conditions*: (a) NaHMDS, THF, –78 °C, 5 min, 63%.

modified Julia olefination of polyene compounds mainly produced the *Z*-isomer at the connected double bond.[3–5,10] In this case, the *E*/*Z* ratio of the obtained mixture was 22 : 78, which was changed in benzene to 83 : 17, 13*E*- to 13*Z*-isomers by 8 days of fluorescent light illumination at room temperature in an argon atmosphere as previously reported.[4,5] We then isolated both compounds and confirmed their structures by an analysis of their NMR (750 MHz) spectra.

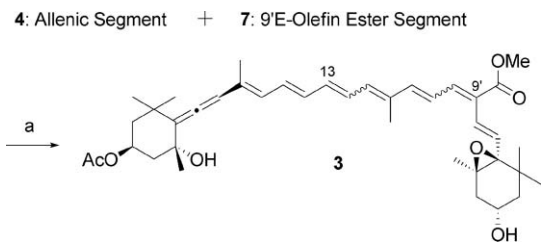
Next was the synthesis of the olefin ester derivative **3**. For the stereocontrolled synthesis of olefin ester half-segment **7**, we attempted the hydrostannylation of alkyne **12**. However, all attempts using typical hydrostannylation conditions were unsuccessful. Meanwhile, the Wittig reaction of aldehyde **10** gave bromide **14**, resulting from lactonization followed by elimination through **14′** (Scheme 3). Then, we tried a one-pot procedure for all three steps to avoid the lactonization; thus, the continuous reactions of butenolide **9** with $^{i}Pr_2NEt$ for the stereocontrolled ring opening, the Wittig reagent, and then methyl iodide to trap the resulting carboxyl anion in one-pot gave the desired bromide **15** as a mixture of 11′*E*/11′*Z* = 1/1 in 69% yield. The Stille cross-coupling of **15** with vinyl stannane **16**[11] afforded tetraene alcohol **17** as a mixture of 9′*E*/9′*Z* = 6/1, whose C11′ position was only *E*. Although we isolated the 9′*E* and 9′*Z* isomer of **17** by HPLC, the desired 9′*Z*-isomer decomposed to a complex mixture within a few days under an argon atmosphere at –20 °C. Since the isolated 9′*Z*-isomer **17** was unstable, the obtained mixture of the alcohol **17** (9′*E*/9′*Z* = 6/1) was transformed into the olefin ester segment **7** by a TBAF treatment followed by MnO_2 oxidation.

We then tried to connect segments **4** and **7** by the modified Julia olefination. The anion derived from **4** was stirred with the mixture of stereoisomers of **7** under the same conditions used for the coupling of **4** and **6** (Scheme 4). The reaction was over within 5 min in the dark to produce the coupling products as a mixture of the stereoisomers in 46% amount, whose HPLC is shown in Fig. 3. The major peak (peak 1) was estimated to be 45% of the mixture by HPLC analysis (other isomers were 16%, 14%, 5%, 5%, and others). Isomerization to the desired all-*trans* **3-3** was attempted under the same conditions used previously. After 5 days, the initially generated major peak (peak 1) changed to another peak (peak 2; 44% based on HPLC analysis) in an equilibrium state. We then isolated both compounds and elucidated their structures by NMR (400 and 750 MHz). This clarified that peak 1 was (13*Z*,9′*E*)-isomer **3-1** and peak 2 was (13*E*,9′*E*)-isomer **3-2** (Fig. 3). Unfortunately, we could not obtain the desired all-*trans* (13*E*,9′*Z*)-isomer **3-3**.

We investigated the stability of the synthesized ring opening derivatives **2** and **3**, and found the isolated all-*trans* acetylene ester derivative **2-1** was more labile than **2-2** (13*Z*-isomer). For instance, the isolated all-*trans* derivative **2-1** (13*E*-isomer) was isomerized to **2′** by a trace amount of hydrochloric acid in $CDCl_3$,



Scheme 3 Synthesis of olefin ester segment **7**. *Reagents and conditions*: (a) $P^{+}Ph_3CH_2BrBr^{-}$, NaHMDS, THF, −30 °C, 5 min; (b) $^{i}Pr_2NEt$, DMSO, r.t., 15 min, then $P^{+}Ph_3CH_2BrBr^{-}$, NaHMDS, THF, −30 °C, 5 min, then MeI, r.t., 15 min, 69%; (c) **16**, $PdCl_2(CH_3CN)_2$, DMSO, 60 °C, 30 min, 50%; (d) TBAF, THF, 45 °C, 3 h, 65%; (e) MnO_2, Et_2O, r.t., 5 min.



Scheme 4 Synthesis of olefin ester derivative **3**. *Reagents and conditions*: (a) NaHMDS, THF, −78 °C, 5 min, 46%.

but the corresponding isomerization of **2-2** (13*Z*-isomer) was not observed (Fig. 4). In addition, the all-*trans* derivative **2-1** rapidly isomerized to the *Z* form upon illumination.[12] This may occur due to the contribution of the carbonyl group of the methyl ester similar to the case of the 9′*E*-olefin ester derivative **3-2**. Furthermore, we tried to construct PCP analogues using the synthesized peridinin derivatives **2** and **3**. First, we attempted to reconstitute the PCP apoprotein using the 9′*E*-olefin ester derivative **3-2** under the same conditions that were successful for peridinin,[13] but reconstitution was not observed. We also tried to reconstitute the apoprotein using the 13*Z*-isomer **2-2**, but it did not bind the protein either.[14] The reason may be that these compounds are bent into a *cis* configuration and therefore, they may not fit properly into the protein binding site. These results

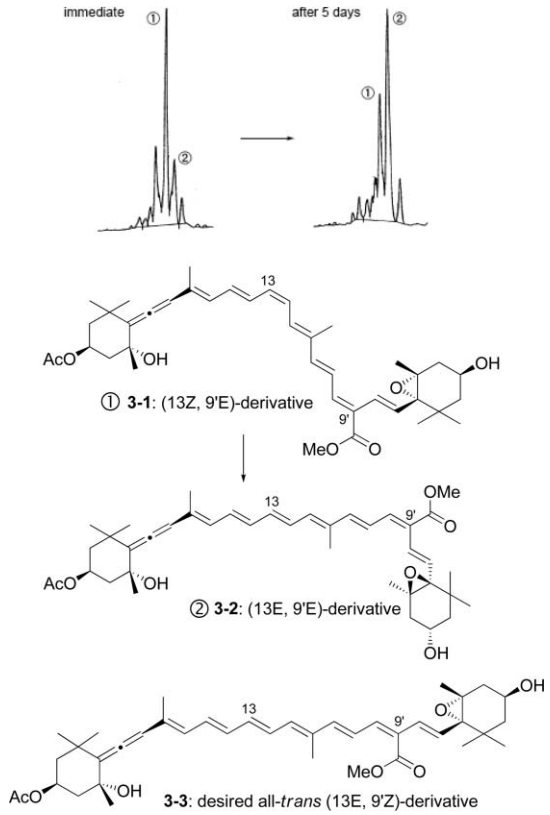


Fig. 3 Isomerization and structure of olefin ester derivative **3**.

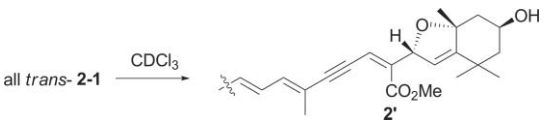


Fig. 4 Characteristics of the acetylene ester derivative **2**.

apparently show that the γ-ylidenbutenolide of peridinin at least contributes to the stereochemical stability of the compound and keeps the all-*trans* conformer suitable for incorporation into the protein to form the PCP complex.

The wavelengths of maximum absorptions (λ_{max}) in the electronic spectra of peridinin (**1**) and the synthesized derivatives **2-1** and **3-2** in hexane are given in Table 1. Peridinin (**1**) shows the longest λ_{max}, and although the 9′*E*-olefin ester derivative **3-2** has seven conjugated carbon–carbon double bonds like peridinin, the open-ring derivative displays a shorter λ_{max} than peridinin (**1**) due to shorter effective π-electron conjugated chain length. We have already reported the results of ultrafast time-resolved optical absorption experiments on these synthesized molecules in solution.[15] In that work the energy barrier for the transfer of

Table 1 Result of UV spectra of peridinin and its derivatives

	λ_{max}/nm
Peridinin (**1**)	454.0
(13*E*,9′*E*)-Olefin ester Derivative **3-2**	430.5
13*E*-Acetylene ester Derivative **2-1**	410.0

population from the initially-populated S_1 state to the ICT state in polar solvent was demonstrated to be affected by the structural modifications.

In summary, we have achieved the synthesis of two different peridinin derivatives whereby the γ-ylidenbutenolide function has been modified. Comparing the stereochemical stability and spectral characteristics of the synthesized ylidenbutenolide modified analogues to those of peridinin has resulted in the conclusion that this particular functional group at least contributes to maintaining the stereochemistry of the conjugated double bonds in the all-*trans* configuration and giving rise to a λ_{max} value desirable for the marine organism to absorb light in the blue–green region of the visible spectrum. The synthesis of another ylidenbutenolide-modified derivative is currently in progress in our laboratory to explore further the role of this unique functional group on the stereochemical and spectral properties of peridinin.

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