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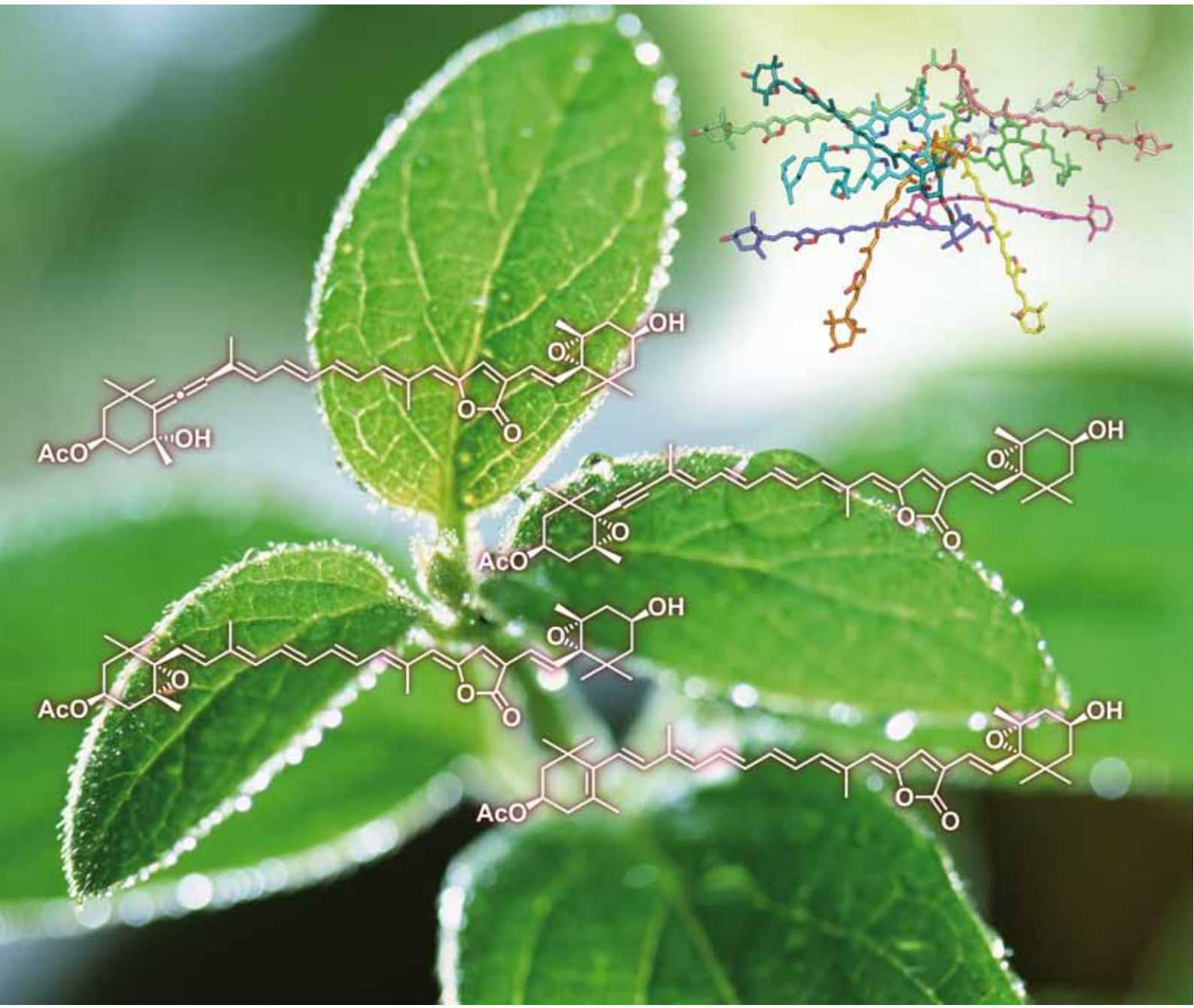

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Syntheses of allene-modified derivatives of peridinin toward elucidation of the effective role of the allene function in high energy transfer efficiencies in photosynthesis†

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Peridinin is known as the main light-harvesting pigment in photosynthesis in the sea and exhibits exceptionally high energy transfer efficiencies to chlorophyll a. This energy transfer efficiency is thought to be related to the intricate structure of peridinin, which possesses allene and ylidenbutenolide functions in the polyene backbone. There are, however, no studies on the relationship between the structural features of peridinin and its super ability for energy transfer. We then focused on the subjects of why peridinin possesses a unique allene group and how the allene function plays a role in the exceptionally high energy transfer. Toward elucidation of the exact role of the allene function, we now describe the syntheses of three relatively unstable allene-modified derivatives of peridinin along with the results of the Stark spectroscopy of peridinin and the synthesized peridinin derivatives.

Introduction

Peridinin (**1**) was first isolated in 1890 from planktonic algae dinoflagellates, which are causally linked to red tides,[1] and displays an atypical C37 carbon skeleton for carotenoids possessing an allene and a ylidenbutenolide function in conjugation with a π-electron conjugated system.[2] This highly functionalized C37-norcarotenoid is a very attractive target molecule for synthetic organic chemists because of both its characteristic structure and its tremendous ability for highly effective energy transfer in photosynthesis. The first total synthesis of enantiomerically pure peridinin was achieved by Ito *et al.* in 1990.[3] We reported the second total synthesis of peridinin in 2002, featuring high stereochemical control of the six asymmetric carbons and the geometry of the seven double bonds in the molecule.[4] The third total synthesis was described by Brückner's group in 2006, employing a novel strategy using (+)-diethyl tartrate and (−)-actinol,[5] and the fourth one was achieved by de Lera's group in 2007, featuring three-component coupling using a dihalogenated C_8 linchpin unit.[6]

This carotenoid has been known as the main light-harvesting pigment in photosynthesis in the sea and forms the peridinin-chlorophyll a (Chl a)-protein (PCP) complex found in dinoflagellates. The crystal structure of the main form of the PCP trimer from *Amphidinium carterae* was determined by X-ray crystallography as shown in Fig. 1.[7] Each of the polypeptides binds eight peridinin molecules and two Chl a molecules, and the allene function of peridinin exists in the center of the PCP. In this complex, a so-called antenna pigment, peridinin exhibits exceptionally high (>95%) energy transfer efficiencies to Chl a.[8] In addition, the presence of an intramolecular charge transfer (ICT) excited state of peridinin has been proposed based on an anomalous strong solvent dependence of its singlet excited state lifetime.[9] This particular excited state is thought to be related to the intricate structure of peridinin, which has allene and ylidenbutenolide functions in the polyene backbone. In particular, the ylidenbutenolide function provides the molecule asymmetry and produces an evident dipole moment in the molecule.[10] Recently, it was proposed that the presence

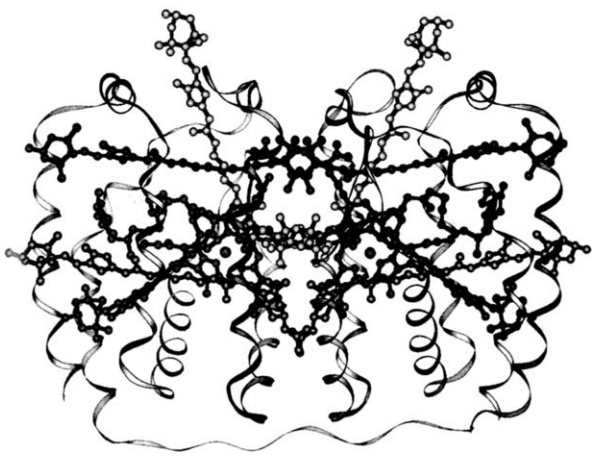

Fig. 1 Crystal structure of PCP complex.

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of the ICT excited state promotes dipolar interactions with Chl a in the PCP complex and facilitates energy transfer *via* a dipole mechanism.[11] Furthermore, the Stark spectroscopy of peridinin was studied to try to determine the change in electrostatic properties produced on excitation within the absorption band.[10] However, the precise nature of the ICT excited state and its role in light-harvesting is not yet entirely clear, and there are no studies on the relation between the structural features of peridinin and its super ability for the energy transfer in the PCP complex. In particular, no studies on the function of the allene group have been reported so far, probably because the synthesis of various kinds of desired peridinin derivatives has not been easy. We have therefore focused on the subjects of why peridinin possesses a unique allene group and how the allene function plays a role in the exceptionally high energy transfer and began with the synthesis of allene-modified derivatives of peridinin.

In order to understand the exact roles of the allene group, we designed the peridinin derivatives B, C, and D. Derivative B (**2**) possesses an epoxy-acetylene, derivative C (**3**) has an epoxy-olefin, and derivative D (**4**) has a conjugating olefin group instead of the hydroxy-allene group (Fig. 2). These derivatives would provide useful information on the roles of the allene group by comparing the Stark spectroscopy and solvent dependence data of their singlet excited state lifetimes with those of peridinin. We now describe the results of the synthetic studies on these peridinin derivatives and their Stark spectroscopy results compared with those of peridinin.

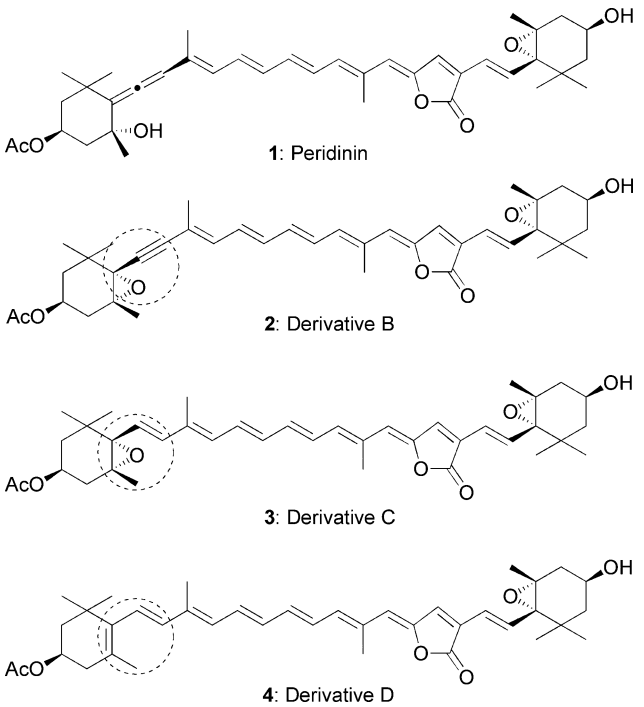


Fig. 2 Structures of peridinin derivatives.

Results

Retrosynthetic analysis

According to the stereocontrolled synthesis of peridinin, which we previously established,[4] we planned to synthesize three peridinin derivatives B, C, and D by coupling between the common ylidenbutenolide half-segment **5**[4] and the corresponding allene-modified half-segments **6**, **7**, and **8** using the modified Julia olefination reaction, respectively (Fig. 3). Both half-segments would be synthesized from the optically homogenous epoxyaldehyde derivative **9**[12] and (–)-vinyltriflate **10**,[3b,c] both of which had been prepared from (–)-actinol. The outline of the synthesis of ylidenbutenolide segment **5** is described in Scheme 1 as reported previously.[4] This synthesis includes a Pd-catalyzed three-step one-pot ylidenbutenolide formation from allylester **13**, which was synthesized from **9** in a stereocontrolled manner.

Synthesis of peridinin derivative B (2)

First, the synthesis of derivative B (**2**) is described. The stereocontrolled synthesis of the epoxyacetylene half-segment **6** is shown in Scheme 2. Acetoxy derivative **15** was prepared starting from (–)-epoxyaldehyde **9** through alcohol **14**[13] in 53% overall yield. Meanwhile, vinyl iodide **17**, which is a component of **6**, was prepared from known ester **16**[4] by DIBAL reduction. The resulting vinyl iodide **17** was not purified because of its instability. Sonogashira cross-coupling[14] between **15** and **17** in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI in diisopropylamine produced the desired alcohol **18** in 80% yield, which was transformed

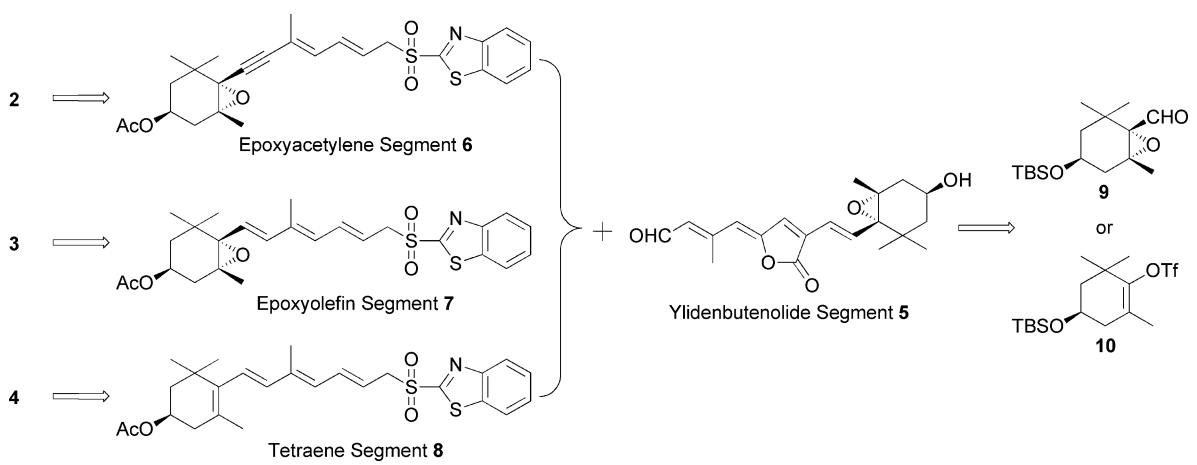
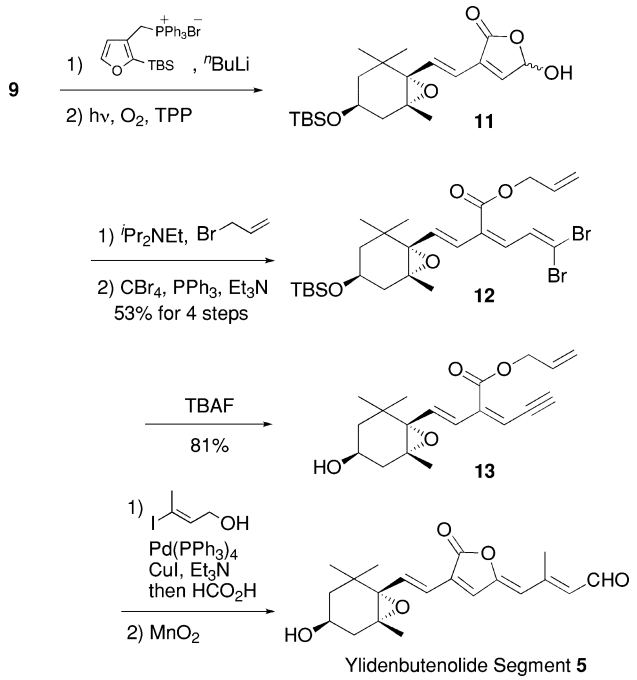
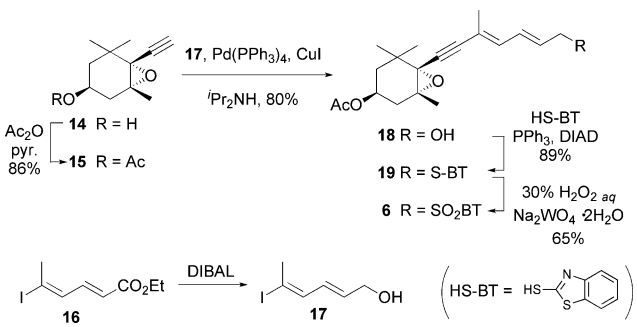


Fig. 3 Retrosynthetic analysis.



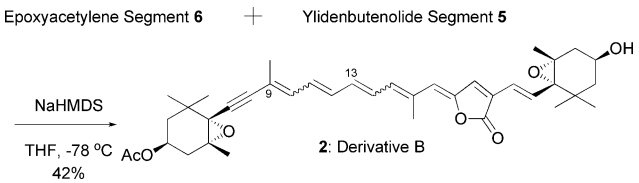
Scheme 1 Synthesis of ylidenbutenolide segment.



Scheme 2 Synthesis of epoxyacetylene segment **6**.

into the acetylene segment **6** using the Mitsunobu reaction with 2-mercaptobenzothiazole, followed by oxidation of the resulting sulfide with aqueous 30% H_2O_2 and $Na_2WO_4 \cdot 2H_2O$.[15] The all-*trans* structure depicted for **6** was confirmed by ^1H NMR spectroscopic analysis.

With epoxyacetylene segment **6** and ylidenbutenolide segment **5** in hand, the crucial modified Julia olefination[16] was explored as the final key step in the synthesis of derivative B (**2**). The reaction of an anion derived from **6** with **5** at −78 °C smoothly proceeded within 5 min in the dark to produce the peridinin derivatives in 42% yield as a mixture of stereoisomers (Scheme 3).



Scheme 3 Synthesis of peridinin derivative B (**2**).

Based on the previous experiments with our carotenoid syntheses[4,17] and the reports of Brückner's and de Lera's groups that the modified Julia olefination of polyene compounds generally produced the Z-isomer at the connected double bond,[18] we tried to isomerize the connected double bond monitoring by HPLC as shown in Fig. 4. The resulting mixture was allowed to stand in benzene at room temperature under fluorescent light in an argon atmosphere. The isomerization under fluorescent light was faster than that in the dark.

After 2 days, we observed that the initially generated major peak (peak 1 in the immediate situation) changed to another major peak (peak 3). After 11 days, while peak 3 gradually decreased, peak 2 increased. After 14 days, peak 2 became the major peak in an equilibrium state. We isolated all peaks by both mobile-phase and reverse-phase HPLC, and elucidated their structures by NMR (400 and 750 MHz). Thus, we clarified that peak 1 was (9E,13Z)-isomer **2**, peak 2 was (9Z,13E)-isomer **2**, and peak 3 was (9E,13E)-all-*trans* derivatve B (**2**). All-*trans* derivative B did not isomerize to the 9Z-isomer at −20 °C but gradually isomerized at room temperature in the dark. Obviously, all-*trans* isomer B was unstable at room temperature and easily isomerized to the 9Z-isomer, which was the most stable isomer[19] and showed a much shorter maximum absorption spectrum (438.0 nm) than that of peridinin (454.0 nm).

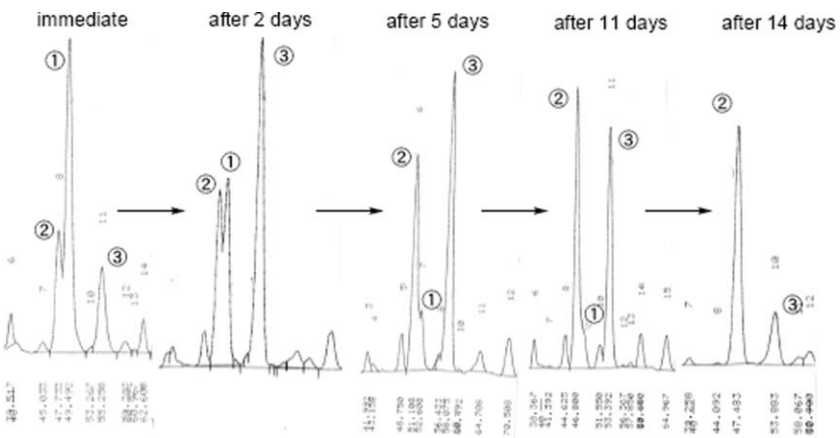
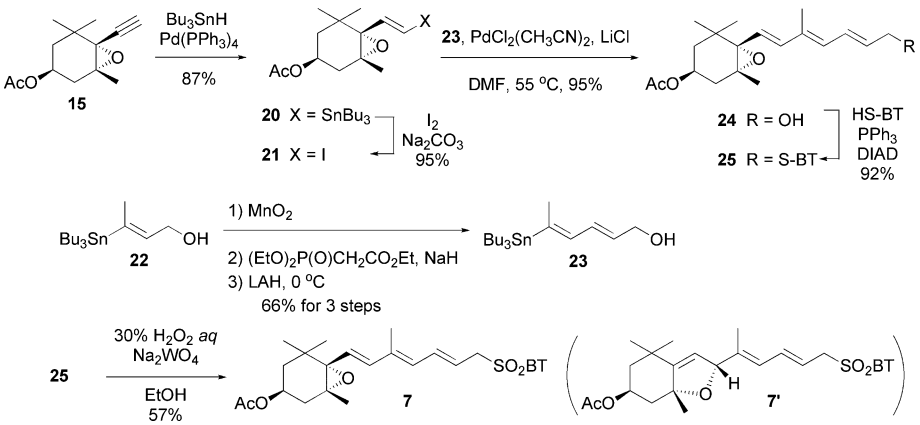


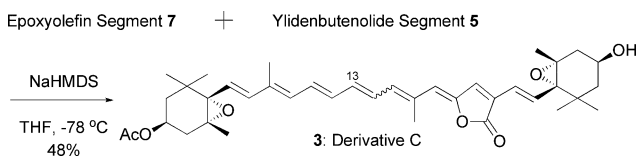
Fig. 4 Isomerization of peridinin derivative B (**2**).



Scheme 4 Synthesis of epoxyolefin segment **7**.

Synthesis of peridinin derivative C (3)

Derivative C (**3**) would be synthesized by the modified Julia olefination of the epoxyolefin segment **7** with the ylidenbutenolide segment **5** (Schemes 4 and 5). The segment **7** would be obtained by a coupling between vinyl iodide **21** and vinylstannane **23**. The Pd-catalyzed hydrostannylation of acetate **15** produced **20** in 87% yield, which was rather better than that of the corresponding alcohol derivative **14** (68%).[6] The obtained stannane **20** was transformed into the corresponding vinyl iodide **21** in excellent yield. Meanwhile, vinyl stannane **23** was prepared by MnO_2 oxidation of **22**[20] followed by the Horner-Emmons reaction and then LAH reduction. The Stille cross-coupling reaction[21] of acetyl iodide **21** with vinyl stannane **23** in the presence of $PdCl_2(CH_3CN)_2$ and LiCl gave the desired alcohol **24** in 95% yield as a single isomer. The Stille cross-coupling of the reversed combination, namely acetyl stannane **20** and vinyl iodide **17**, did not produce a desirable result. The alcohol **24** was transformed into sulfide **25** under Mitsunobu reaction conditions in excellent yield. Oxidation of **25** using the same reagents as for the preparation of **6** (30% H_2O_2 and Na_2WO_4) gave the desired **7**. However, the use of 30% H_2O_2 and $(NH_4)_6Mo_7O_{24}$ gave a mixture of **7** and **7′** in low yield, and the ratio was not reproducible (1–4 : 1). It is noteworthy that sulfone **7** was easily isomerized to **7′** by trace amounts of hydrochloric acid in $CDCl_3$.



Scheme 5 Synthesis of peridinin derivative C (**3**).

The desired **7** was reacted with the ylidenbutenolide segment **5** under the same modified Julia olefination reaction condition as in the case of derivative B to produce a mixture composed of two major components in mobile phase HPLC (acetone/hexane = 1/10). Each of them proved to be structural isomers by mass spectroscopy and showed very similar absorption spectra instead of a peak at around 310 nm absorption, which was usually assigned to the Z-configuration.[22] In order to isomerize at the connected double bond and to obtain the desired all-*trans* isomer **3**, the mixture was allowed to stand for 2 days under the same conditions as in the case of derivative B (**2**). In the HPLC of the isomerized mixture, we observed that the initially produced major component (peak 1) clearly changed to another one (peak 2), and peak 2 finally comprised more than 79% of the mixture (Fig. 5). We then isolated both peaks 1 and 2 and elucidated their structures by NMR (400 and 750 MHz). The structure of peak 2 was assigned to the all-*trans* derivative C (**3**) by rigorous analysis of coupling constants and NOE experiments (750 MHz), and peak 1 was also the 13Z-isomer. The electronic spectrum of derivative C (**3**) showed a maximum absorption (450.0 nm) similar to that of peridinin (454.0 nm).

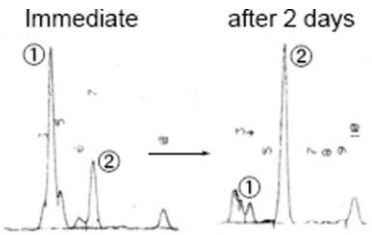
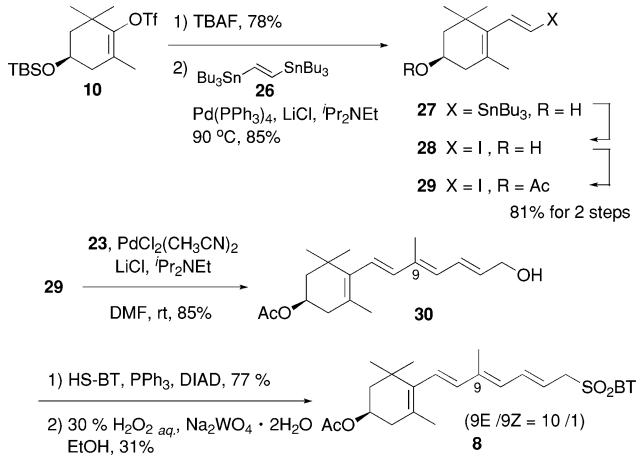


Fig. 5 Isomerization of peridinin derivative C (**3**).

Synthesis of peridinin derivative D (4)

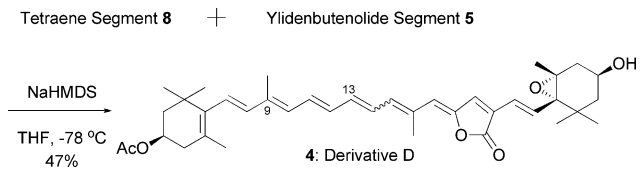
Next was the synthesis of derivative D (**4**), which has no epoxide and possesses nine conjugating double bonds compared with the eight conjugating feature of peridinin. Stille coupling of the corresponding alcohol derived from vinyl triflate **10** with bisstannane **26**[23] in the presence of catalytic amounts of $Pd(PPh_3)_4$ and LiCl proceeded smoothly, and the desired coupling product **27** was obtained in 85% yield (Scheme 6). The obtained stannane **27** was transformed into the corresponding vinyl iodide followed by acetylation to produce **29** in 81% yield over two steps. The second Stille cross-coupling of **29** with vinyl stannane **23**, which was used in the synthesis of **3**, afforded tetraene alcohol **30** as a single isomer. In this coupling, the reaction proceeded smoothly at room temperature, and the absence of $^{i}Pr_2NEt$ gave a mixture with the 9Z-isomer of **30** in a ratio of eight to one by NMR. The amount of 9Z-isomer seemed to increase at higher reaction temperature, for instance, 9E/9Z = 3/1 at 50 °C. The desired



Scheme 6 Synthesis of tetraene segment **8**.

sulfone **8** was obtained from **30** by the Mitsunobu reaction with 2-mercaptobenzothiazole, followed by oxidation of the resulting sulfide with aqueous 30% H_2O_2 and $Na_2WO_4{\cdot}2H_2O$,[15] as a mixture of 9E/9Z = 10/1 in 31% yield. The use of 30% H_2O_2 and $(NH_4)_6Mo_7O_{24}$, and mCPBA gave a complex mixture. Oxidation of allylic sulfide to the corresponding sulfone in conjugated polyenes was still problematic.

As shown in Scheme 7, the modified Julia olefination between sulfone **8** and aldehyde **5** proceeded successfully, and the reaction was over within 5 min in the dark to produce the coupling products as a mixture of stereoisomers in almost 47% yield, in which peak 1 was estimated to comprise 60% by HPLC analysis (Fig. 6). Isomerization was again attempted under the same conditions. After 4 days, a large amount of peak 1, which was a major component of the mixture immediately after the reaction, changed to peak 2 (peak 2 : peak 1 > 3 : 1 based on HPLC analysis). The peak 3, presumed to be a 9Z-isomer, nearly disappeared after 4 days. The compound of peak 2 was isolated by mobile and reverse phase HPLC and its structure was elucidated by NMR



Scheme 7 Synthesis of peridinin derivative D (**4**).

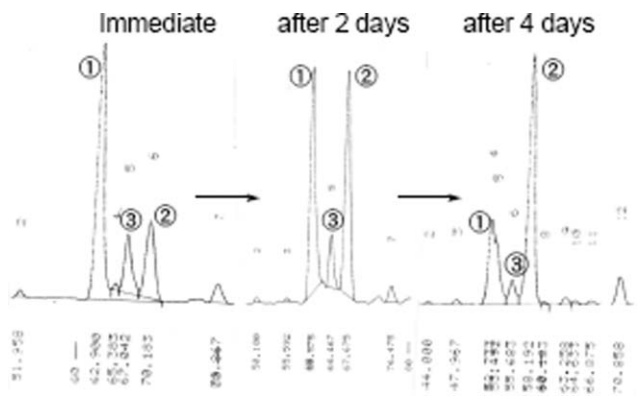


Fig. 6 Isomerization of peridinin derivative D (**4**).

Table 1 Results of UV and Stark spectra of peridinin and its derivatives

	λ_{max} (nm)	$\lvert\Delta\mu\rvert$ ($\times10^{-29}$ C·m)
Peridinin	454.0	5.42
Derivative B (**2**)	438.0	2.47
Derivative C (**3**)	450.0	4.22
Derivative D (**4**)	459.0	4.25

(400 and 750 MHz) to be the desired all-*trans* isomer **4**. The obtained derivative D (**4**) showed the maximum absorption at 459.0 nm, which was similar to that of peridinin. The synthesized **4** was, however, rather unstable and was gradually decomposed within one week at room temperature under argon atmosphere. In contrast, peridinin could be stored without notable decomposition after ten days under similar circumstances.

Results of Stark measurement

The maximum absorptions of the electronic spectra of peridinin (**1**) and the synthesized derivatives (**2–4**) in hexane are summarized in Table 1. Evidently, derivative D showed the longest λ_{max}. Next, the Stark spectra of peridinin (**1**) and the derivatives B-D (**2–4**) were obtained. Stark spectra can determine the change in electrostatic properties and estimate the change in the static dipole moment ($\lvert\Delta\mu\rvert$) between the ground state and the excited state. The large dipole moment would allow for strong dipolar interaction between peridinin and Chl a in PCP, and would contribute to high energy transfer.[10] The Stark spectra of peridinin and derivatives B, C and D were recorded in methyl methacrylate polymer at 77 K and the results are listed in Table 1.[24] The $\lvert\Delta\mu\rvert$ values were corresponding to the CT absorption band. As a result, peridinin showed the largest $\lvert\Delta\mu\rvert$ value among all of them. Namely, peridinin yielded a $\lvert\Delta\mu\rvert$ value of 5.42 ($\times10^{-29}$ C·m), derivative B (**2**) showed 2.47, derivative C (**3**) showed 4.22, and derivative D (**4**) showed 4.25. The $\lvert\Delta\mu\rvert$ value of peridinin is in agreement with that of Grondelle's group.[10] The difference in the $\lvert\Delta\mu\rvert$ values is evidently attributable to the difference in the functional groups. Although peridinin possesses fewer conjugating double bonds and shows a shorter λ_{max} than derivative D, the $\lvert\Delta\mu\rvert$ value of peridinin is the largest among the four compounds. Thus, we have understood that the unique allene group contributes to production of the large dipole moment in the molecule. These results strongly suggest that the allene group of peridinin is essential for formation of the effective ICT state, which would allow the quantitative energy transfer to Chl a in the PCP complex. The exact role of the allene function for the large $\lvert\Delta\mu\rvert$ value is under investigation from a spectroscopic point of view.[24]

Conclusion

In summary, we synthesized three kinds of relatively unstable allene-modified derivatives of peridinin, derivatives B, C, and D, which respectively possessed an epoxy-acetylene, an epoxy-olefin, and a conjugating olefin groups instead of the allene group. In addition, the Stark spectra of peridinin and these derivatives were obtained, and showed that the $\lvert\Delta\mu\rvert$ value of peridinin was the largest among the four compounds. These results apparently show that the allene group of peridinin effectively contributes to production of the large dipole moment in the molecule, which

would result in the high energy transfer efficiencies to Chl a in the PCP complex. Ultrafast time-resolved optical absorption spectroscopic experiments in addition to Stark spectroscopy of the synthesized compounds are currently in progress to further understand the exact role of the allene group.

Experimental

General synthetic procedures

All commercially available reagents were used without further purification. All solvents were used after distillation. Tetrahydrofuran (THF), diethyl ether, benzene, toluene, and dimethoxyethane (DME) were refluxed over and distilled from sodium-benzophenone ketyl. Dichloromethane was refluxed over and distilled from P_2O_5. Dimethylformamide (DMF) was distilled from CaH_2 under reduced pressure. Triethylamine, diisopropylamine, and diisopropylethylamine were refluxed over and distilled from KOH. Preparative separation was performed by column chromatography on silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz and 750 MHz spectrometers, and chemical shifts were represented as δ values relative to the internal standard TMS. IR spectra were recorded on a FT-IR Spectrometer. High-resolution mass spectra (HRMS) were measured on a ESI-TOF MS.

(1*S*,2*R*,4*S*)-4-Acetoxy-1,2-epoxy-1-ethynyl-2,6,6-trimethylcyclohexanol (15). To a solution of acetylene **14** (215 mg, 1.21 mmol) in pyridine (5 mL) was added acetic anhydride (0.18 mL, 1.94 mmol) at room temperature and the reaction mixture was stirred for 18 h at the same temperature. A saturated aqueous $CuSO_4$ solution was added, and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by silica gel column chromatography (5% ethyl acetate in hexane) afforded acetate **15** (209 mg, 77%): $[\alpha]^{24.0}_D$ −20.3 (*c* 1.18, $CHCl_3$); IR (neat, cm^{-1}) 3281, 2966, 2930, 2872, 1738, 1460, 1367, 1242, 1157, 1105, 1043; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.85 (m, 1H), 2.42 (s, 1H), 2.37 (dd, *J* = 15.1, 5.7 Hz, 1H), 2.01 (s, 3H), 1.79 (dd, *J* = 15.1, 6.4 Hz, 1H), 1.60 (dd, *J* = 13.8, 3.4 Hz, 1H), 1.52 (s, 3H), 1.38 (dd, *J* = 13.5, 8.24 Hz, 1H), 1.27 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 80.2, 74.2, 66.9, 64.9, 63.1, 39.7, 35.6, 33.5, 28.4, 25.9, 21.7, 21.3; ESI-HRMS *m*/*z* calcd for $C_{13}H_{18}O_3Na$ $(M + Na)^+$ 245.1154, found 245.1164.

(2*E*,4*E*)-7-[(1′*S*,2′*R*,4′*S*)-4′-Acetoxy-1′,2′-epoxy-2′,6′,6′-trimethylcyclohexa-1′-yl]5-methylhepta-2,4-diene-6-yn-1-ol (18). To a solution of ester **16** (1.11 g, 1.89 mmol) in dichloromethane (18.9 mL) was added dropwise diisobutylaluminium hydride (1.0 M in toluene, 4.56 mL, 4.56 mmol) at −78 °C. After the reaction mixture was stirred for 5 min at the same temperature, aqueous potassium sodium (+)-tartrate tetrahydrate solution was added and then resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.*to afford crude vinyl iodide **17**, which was used to the next reaction without further purification.

To a solution of crude vinyl iodide **17** and acetylene **15** (420 mg, 1.89 mmol) in diisopropylamine (9.45 mL) was added tetrakis(triphenylphosphine)palladium (262 mg, 0.23 mmol) and CuI (40 mg, 0.21 mmol). After being stirred for 1.5 h at room temperature, the reaction mixture was poured into a saturated aqueous NH_4Cl solution, and then the resulting mixture was extracted with diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by silica gel column chromatography (from 30% to 50% ethyl acetate in hexane) afforded the conjugated acetylene derivative **18** (484 mg, 81%): $[\alpha]^{24.0}_D$ +15.1 (*c* 1.07, $CHCl_3$); IR (neat, cm^{-1}) 3458, 2965, 2926, 1738, 1448, 1370, 1244, 1043; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.50 (dd, *J* = 14.8, 11.4 Hz, 1H), 6.39 (d, *J* = 11.2 Hz, 1H), 5.90 (dt, *J* = 14.9, 5.5 Hz, 1H), 4.87 (m, 1H), 4.23 (d, *J* = 5.5 Hz, 2H), 2.38 (dd, *J* = 14.9, 5.7 Hz, 1H), 2.01 (s, 3H), 1.91 (s, 3H), 1.80 (dd, *J* = 14.8, 6.4 Hz, 1H), 1.62 (dd, *J* = 13.8, 3.5 Hz, 1H), 1.51 (s, 3H), 1.39 (dd, *J* = 13.5, 8.3 Hz, 1H), 1.27 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 135.4, 134.2, 125.9, 118.0, 89.3, 85.5, 67.1, 65.6, 63.9, 62.9, 39.8, 35.7, 34.0, 28.6, 26.1, 21.9, 21.3, 17.4; ESI-HRMS *m*/*z* calcd for $C_{19}H_{26}O_4Na$ $(M + Na)^+$ 341.1729, found 341.1740.

2-(((2′*E*,4′*E*)-7′-((1″*S*,2″*R*,4″*S*)-4″-Acetoxy-1″,2″-epoxy-2″,6″,6″-trimethylcyclohexylidene-1″-yl)-5′-methylhepta-2,4-diene-6-yn)sulfanyl)benzothiazole (19). To a solution of **18** (100 mg, 0.31 mmol), 2-mercaptobenzothiazole (68 mg, 0.41 mmol) and triphenylphosphine (107 mg, 0.41 mmol) in THF (4 mL) was added dropwise diisopropyl azodicarboxylate (0.09 mL, 0.44 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and all solvents were removed *in vacuo.* To the residue was added diethyl ether and the precipitate was removed by filtration through a pad of Celite to give the crude products as a solution, which was concentrated *in vacuo.* Purification by short silica gel column chromatography (from 5% to 10% ethyl acetate in hexane) afforded the thioether **19** (127 mg, 87%): $[\alpha]^{26.0}_D$ +8.5 (*c* 0.97, $CHCl_3$); IR (neat, cm^{-1}) 2967, 2926, 1736, 1460, 1427, 1367, 1242, 1042; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (m, 1H), 7.75 (m, 1H), 7.42 (m, 1H), 7.30 (m, 1H), 6.60 (dd, *J* = 14.9, 11.2 Hz, 1H), 6.36 (d, *J* = 11.5 Hz, 1H), 5.93 (m, 1H), 4.87 (m, 1H), 4.08 (d, *J* = 7.6 Hz, 2H), 2.37 (ddd, *J* = 14.9, 5.7, 0.9 Hz, 1H), 2.00 (s, 3H), 1.89 (s, 3H), 1.79 (dd, *J* = 15.1, 6.6 Hz, 1H), 1.61 (m, 1H), 1.48 (s, 3H), 1.38 (dd, *J* = 13.7, 8.2 Hz, 1H), 1.24 (s, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 165.8, 153.2, 135.4, 135.0, 129.8, 128.9, 126.1, 124.3, 121.5, 120.9, 118.9, 89.2, 86.1, 67.1, 65.6, 63.9, 39.9, 35.9, 34.1, 28.7, 26.2, 21.9, 21.4, 17.5, –0.02; ESI-HRMS *m*/*z* calcd for $C_{26}H_{29}NO_3S_2Na$ $(M + Na)^+$ 490.1487, found 490.1467.

2-(((2′*E*,4′*E*)-7′-((1″*S*,2″*R*,4″*S*)-4″-Acetoxy-1″,2″-epoxy-2″,6″,6″-trimethylcyclohexylidene-1″-yl)-5′-methylhepta-2,4-diene-6-yn)sulfonyl)benzothiazole (6). To a solution of the thioether **19** (133 mg, 0.28 mmol) in ethanol (3 mL) was added dropwise a solution of ammonium heptamolybdate tetrahydrate (527 mg, 0.43 mmol) in hydrogen peroxide (30 wt.% in water, 1.4 mL) at 0 °C. After being stirred for 30 min at room temperature, the reaction mixture was poured into water and then extracted with diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by short silica gel column chromatography afforded the sulfone **6** (from 10% to 20% ethyl acetate in hexane) (79 mg, 58%): $[\alpha]^{24.0}_D$ +9.6 (*c* 0.29, $CHCl_3$); IR (neat, cm^{-1}) 2967, 2928, 1736, 1472, 1368, 1333, 1244, 1150, 1028; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (m, 1H),

8.02 (m, 1H), 7.64 (m, 2H), 6.46 (dd, $J = 14.9$, 11.5 Hz, 1H), 6.31 (d,$J = 11.4$ Hz, 1H), 5.69 (m, 1H), 4.87 (m, 1H), 4.31 (d, $J =$ 7.8 Hz, 2H), 2.37 (dd, $J = 15.1$, 5.7 Hz, 1H), 2.01 (s, 3H), 1.78 (dd, $J = 15.1$, 6.4 Hz, 1H), 1.72 (s, 3H), 1.60 (m, 1H), 1.47 (s, 3H), 1.37 (dd, $J = 13.7$, 8.4 Hz, 1H),1.23 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 165.4, 152.6, 135.7, 134.0, 128.1, 127.7, 125.4, 122.4, 121.5, 117.7, 88.7, 87.3, 67.1, 65.7, 63.8, 58.7, 39.9, 35.8, 34.1, 28.6, 26.2, 21.9, 21.4, 17.5, –0.02; ESI-HRMS *m/z* calcd for $C_{26}H_{29}NO_5S_2Na$ $(M + Na)^+$ 522.1385, found 522.1381.

Peridinin derivative B (2). To a solution of acetylene segment **6** (22 mg, 0.044 mmol) and ylidenbutenolide segment **5** (15 mg, 0.044 mmol) in THF (0.87 mL) was added dropwise sodium bis(trimethylsilyl)amide (1.0M in THF, 0.12 mL, 0.12 mmol) at −78 °C in the dark. After being stirred for 5 min at the same temperature, the reaction mixture was poured into water and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by short silica gel column chromatography (from 30% to 50% ethyl acetate in hexane) in the dark afforded peridinin derivative **2** (5 mg, 18%) as a mixture of the isomers as a red film. A solution of a mixture of all-*trans*-peridinin derivative **2** and its *cis*-isomer in benzene was left at room temperature under the fluorescence light. After 11 days, partial separation by preparative HPLC [column: Develosil CN-UG (0.6 × 25 cm); mobile phase: acetone/*n*-hexane = 1/10; flow rate: 2.0 mL/min; UVdetect: 438 nm; retention time: (all-*trans* isomer) 51 min, (9Z, 13E-isomer) 58 min] in the dark, and HPLC [column: YMC Carotenoid C30 (10 × 250 mm); reverse phase: acetonitrile/methanol/water = 50/48/2; flow rate: 2.0 mL/min; UV detect: 438 nm; retention time: (all-*trans* isomer) 22 min] in the dark, was afforded the desired optically active peridinin derivative **2** as a red film: IR (neat, cm^{-1}) 3455, 2924, 2853, 2367, 1701, 1655, 1561, 1460, 1419, 1379, 1259, 1121, 1041; ^{1}H NMR (C_6D_6, 750 MHz) δ 7.57 (d, $J = 15.5$ Hz, 1H), 6.61 (d, $J = 11.7$ Hz, 1H), 6.56 (d, $J = 15.5$ Hz, 1H), 6.42 (dd, $J = 13.9$, 12.3 Hz, 1H), 6.38 (dd, $J = 14.3$, 12.1 Hz, 1H), 6.30 (d, $J = 11.8$ Hz, 1H), 6.26 (dd, $J = 14.2$, 11.5 Hz, 1H), 6.15 (s, 1H), 6.13 (dd, $J = 14.2$, 11.7 Hz, 1H), 5.18 (s, 1H), 5.07 (m, 1H), 3.75 (m, 1H), 2.25 (dd, $J = 14.8$, 3.5 Hz, 1H), 2.20 (ddd, $J = 14.5$, 4.2, 1.0 Hz, 1H), 2.11 (s, 3H), 1.79 (s, 3H), 1.68 (s, 3H), 1.62 (m, 1H), 1.46 (s, 3H), 1.41 (m, 2H), 1.35 (m, 1H), 1.34 (s, 3H), 1.31 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 1.06 (m, 1H); ^{13}C NMR (C_6D_6, 188 MHz) δ 169.3, 168.3, 147.7, 137.3,136.8, 136.4, 136.3, 135.1, 135.0, 134.9, 130.9, 130.0, 125.4, 122.3, 119.5, 118.2, 90.1, 89.1, 70.5, 67.4, 67.2, 65.6, 64.1, 63.9, 47.3, 41.1, 40.4, 36.2, 35.3, 34.4, 29.5, 29.0, 26.6, 25.3, 22.1, 20.9, 19.9, 17.7, 15.6; ESI-HRMS *m/z* calcd for $C_{39}H_{48}O_7Na$ $(M + Na)^+$ 651.3298, found 651.3276.

***trans*-2-[(1′*S*,2′*R*,4′*S*)-4′-Acetoxy-1′,2′-epoxy-2′,6′,6′-trimethylcyclohexyl]-1-(tributylstannyl)ethylene (20).** To a solution of acetylene **15** (649 mg, 2.92 mmol), tetrakis(triphenylphosphine)palladium (169 mg, 0.15 mmol) in THF (29 mL) was added dropwise tributyltin hydride (1.55 mL, 5.84 mmol) at –78 °C. After being stirred for 15 min at room temperature and the reaction mixture was filtered through a pad of silica gel to give the crude products as a solution, which was concentrated *in vacuo.* Purification by silica gel column chromatography afforded **20** (1.31 g, 87%): $[\alpha]^{23.0}_D$ –49.44 (*c* 0.89, $CHCl_3$); IR (neat, cm^{-1}) 3466, 2959, 2926, 2872, 2854, 1739, 1462, 1419, 1377, 1365, 1242, 1184, 1155, 1118, 1097, 1070, 1030; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.23 (d, $J = 19.0$ Hz, 1H), 6.16 (d, $J = 19.2$ Hz, 1H), 4.92 (m, 1H), 2.38 (dd, $J = 14.8$, 5.7 Hz, 1H), 2.01 (s, 3H), 1.75 (dd, $J =$ 14.8, 6.8 Hz, 1H), 1.64 (dd, $J = 13.2$, 3.4 Hz, 1H), 1.49 (m, 6H), 1.35 (m, 1H), 1.30 (m, 6H), 1.19 (s, 3H), 1.16 (s, 3H), 0.97 (s, 3H), 0.88 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 142.1, 132.4, 72.2, 67.9, 64.7, 41.5, 36.8, 34.3, 29.2, 28.6, 27.3, 25.5, 21.5, 20.3, 13.8, 9.6; ESI-HRMS *m/z* calcd for $C_{25}H_{46}O_3SnNa$ $(M + Na)^+$ 537.2371, found 537.2363.

***trans*-2-[(1*S*,2*R*,4*S*)-4-Acetoxy-1,2-epoxy-2,6,6-trimethylcyclohexyl]-1-iodoethylene (21).** To a solution of iodine (445 mg, 1.75 mmol) and Na_2CO_3 (372 mg, 3.51 mmol) in dichloromethane (7 mL) was added dropwise a solution of **20** (450 mg, 0.88 mmol) in dichloromethane (2 mL) at 0 °C. After stirring for 5 min at 0 °C, the mixture was poured into a saturated aqueous $Na_2S_2O_3$ solution and then extracted with chloroform. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by silica gel column chromatography afforded iodide **21** (273 mg, 89%): $[\alpha]^{23.0}_D$ –68.0 (*c* 1.01, $CHCl_3$); IR (neat, cm^{-1}) 2965, 2932, 1736, 1603, 1468, 1365, 1242, 1032; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.77 (d, $J = 14.2$ Hz, 1H), 6.28 (d, $J = 14.2$ Hz, 1H), 4.89 (m, 1H), 2.37 (dd, $J = 14.9$, 5.5 Hz, 1H), 2.01 (s, 3H), 1.76 (dd, $J = 15.1$, 6.8 Hz, 1H), 1.63 (dd, $J = 13.5$, 3.4 Hz, 1H), 1.35 (dd, $J = 13.5$, 8.9 Hz, 1H), 1.22 (s, 3H), 1.15 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 141.3, 79.8, 72.5, 67.3, 65.1, 41.3, 36.6, 34.3, 28.4, 25.4, 21.5, 20.2; ESI-HRMS *m/z* calcd for $C_{13}H_{19}IO_3Na$ $(M + Na)^+$ 373.0277, found 373.0277.

Ethyl (2*E*,4*E*)-5-(tributylstannyl)hexa-2,4-dienate (22a). A mixture of **22** (1.0 g, 2.77 mmol) and manganese dioxide (16.6 g) in THF (17 mL) was stirred at room temperature for 6 h. The precipitate was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford crude aldehyde, which was used in the next reaction without further purification.

To a solution of triethyl phosphonoacetate (0.72 mL, 3.6 mmol) in THF (13 mL) was added sodium hydride (133 mg, 3.32 mmol) at 0 °C and the mixture was stirred for 10 min. To this mixture was added a solution of the crude aldehyde in THF (3 mL) at 0 °C. After being stirred for 5 min at room temperature, the reaction mixture was poured into water and then extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by silica gel column chromatography afforded ethyl ester **22a** (936 mg, 79% for 2 steps): IR (neat, cm^{-1}) 2961, 2928, 2870, 2852, 1716, 1620, 1462, 1419, 1367, 1340, 1304, 1265, 1234, 1180, 1132, 1095, 1076, 1043; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (dd, $J = 15.3$, 11.2 Hz, 1H), 6.34 (d, $J = 11.3$ Hz, 1H), 5.79 (d, $J = 15.1$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8, 157.9, 137.6, 136.5, 119.9, 60.1, 29.0, 27.3, 20.6, 14.3, 13.6, 9.2; ESI-HRMS *m/z* calcd for $C_{20}H_{38}O_2SnNa$ $(M + Na)^+$ 453.1795, found 453.1777.

(2*E*,4*E*)-5-(Tributylstannyl)hexa-2,4-dien-1-ol (23). To a suspension of lithium aluminium hydride (36 mg, 0.95 mmol) in THF (6 mL) was added dropwise a solution of **22a** (338 mg, 0.79 mmol) in THF (2 mL) at 0 °C. After being stirred for 10 min at the same temperature, Rochelle salt was carefully added. The reaction mixture was stirred for 30 min at room temperature and then

extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography afforded **23** (223 mg, 73%): IR (neat, cm^{-1}) 3327, 2957, 2920, 2852, 1460, 1417, 1375, 1340, 1292, 1089, 1005; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.64 (dd, J = 15.1, 10.5 Hz, 1H), 6.19 (d, J = 10.5 Hz, 1H), 5.78 (dt, J = 14.8, 5.9 Hz, 1H), 4.22 (t, J = 5.8 Hz, 2H), 2.00 (s, 3H), 1.49 (m, 6H), 1.30 (m, 6H), 0.89 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.2, 138.0, 130.9, 126.3, 63.7, 29.2, 27.5, 19.9, 13.8, 9.2.

(2*E*,4*E*,6*E*)-7-[(1′*S*,2′*R*,4′*S*)-4′-Acetoxy-1′,2′-epoxy-2′,6′,6′-trimethylcyclohexa-1′-yl]-5-methylhepta-2,4,6-trien-1-ol (24). To a solution of iodide **21** (560 mg, 1.6 mmol) and (2*E*,4*E*)-5-(tributylstannyl)hexa-2,4-dien-1-ol **23** (915 mg, 2.40 mmol) in DMF (8 mL) was added bis(acetonitrile)dichloropalladium(II) (21 mg, 0.05 mmol) and lithium chloride (136 mg, 3.20 mmol). After being stirred for 10 min at 55 °C, the reaction mixture was poured into water and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography afforded coupling product **24** (482 mg, 94%) as a yellow oil: $[\alpha]^{23.0}_D$ –41.6 (*c* 1.02, $CHCl_3$); IR (neat, cm^{-1}) 3443, 2964, 2928, 1736, 1450, 1365, 1244, 1030; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.60 (dd, J = 14.2, 10.3 Hz, 1H), 6.27 (d, J = 15.8 Hz, 1H), 6.10 (d, J = 11.2 Hz, 1H), 5.88 (d, J = 15.8 Hz, 1H), 5.86 (m, 1H), 4.93 (m, 1H), 4.24 (m, 2H), 2.40 (dd, J = 15.1, 5.8 Hz, 1H), 2.01 (s, 3H), 1.88 (s, 3H), 1.77 (dd, J = 14.8, 6.8 Hz, 1H), 1.66 (dd, J = 13.2, 3.4 Hz, 1H), 1.34 (m, 1H), 1.18 (s, 3H), 1.15 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 137.4, 134.5, 132.8, 130.4, 127.5, 123.7, 70.3, 67.7, 65.5, 63.5, 41.4, 36.8, 34.7, 28.6, 25.5, 21.4, 20.2, 12.8; ESI-HRMS *m*/*z* calcd for $C_{19}H_{28}O_4Na$ $(M + Na)^+$ 343.1885, found 343.1883.

2-(((2′*E*,4′*E*,6′*E*)-7′-((1″*S*,2″*R*,4″*S*)-4″-Acetoxy-1″,2″-epoxy-2″,6″,6″-trimethylcyclohexylidene-1″-yl)-5′-methylhepta-2,4,6-triene)sulfanyl)benzothiazole (25). To a solution of **24** (330 mg, 1.03 mmol), 2-mercaptobenzothiazole (241 mg, 1.44 mmol) and triphenylphosphine (378 mg, 1.44 mmol) in THF (10 mL) was added dropwise diisopropyl azodicarboxylate (0.32 mL, 1.65 mmol) at 0 °C. The reaction mixture was stirred for 10 min at room temperature and the all solvents were removed *in vacuo*. To a residue was added diethyl ether and the precipitate was removed by filtration through a pad of Celite to give the crude products as a solution, which was concentrated *in vacuo*. Purification by short silica gel column chromatography afforded the thioether **25** (444 mg, 92%): $[\alpha]^{23.0}_D$ –25.6 (*c* 1.08, $CHCl_3$); IR (neat, cm^{-1}) 2964, 2926, 1734, 1460, 1427, 1365, 1242, 1028; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.87 (m, 1H), 7.75 (m, 1H), 7.40 (m, 1H), 7.28 (m, 1H), 6.71 (dd, J = 14.7, 11.3 Hz, 1H), 6.24 (d, J = 15.5 Hz, 1H), 6.07 (d, J = 11.4 Hz, 1H), 5.88 (d, J = 15.5 Hz, 1H), 5.86 (m, 1H), 4.93 (m, 1H), 4.11 (d, J = 7.5 Hz, 2H), 2.38 (dd, J = 15.8, 5.7 Hz, 1H), 2.01 (s, 3H), 1.87 (s, 3H), 1.76 (dd, J = 14.8, 6.8 Hz, 1H), 1.65 (dd, J = 13.2, 3.4 Hz, 1H), 1.33(m, 1H), 1.16 (s, 3H), 1.14 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 166.1, 153.2, 137.2, 135.3, 134.9, 130.9, 129.9, 127.4, 125.9, 124.2, 124.1, 121.5, 120.9, 70.3, 67.6, 65.5, 41.4, 36.7, 36.1, 34.7, 28.5, 25.5, 21.4, 20.2, 12.8; ESI-HRMS *m*/*z* calcd for $C_{26}H_{31}NO_3S_2Na$ $(M + Na)^+$ 492.1643, found 492.1640.

2-(((2′*E*,4′*E*,6′*E*)-7′-((1″*S*,2″*R*,4″*S*)-4″-Acetoxy-1″,2″-epoxy-2″,6″,6″-trimethylcyclohexylidene-1″-yl)-5′-methylhepta-2,4,6-triene)sulfonyl)benzothiazole (7). To a solution of the thioether **25** (30 mg, 0.064 mmol) in ethanol (0.64 mL) was added dropwise a solution of sodium tungstate(VI) dihydrate (42 mg, 0.128 mmol) in hydrogen peroxide (30 wt.% in water, 0.51 mL) at 0 °C. After being stirred for 50 min at room temperature, the reaction mixture was poured into water and then extracted with diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by short silica gel column chromatography afforded the sulfone **7** (18 mg, 56%) as a yellow solid: $[\alpha]^{24.0}_D$ –22.5 (c 0.79, $CHCl_3$); IR (neat, cm^{-1}) 3471, 2930, 2865, 1736, 1637, 1473, 1381, 1334, 1240, 1147, 1116, 976, 763; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.22 (d, J = 7.8 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.65 (m, 2H), 6.59 (dd, J = 14.7, 11.0 Hz, 1H), 6.20 (d, J = 15.6, 1H), 6.02 (d, J = 15.6 Hz, 1H), 5.90 (d, J = 15.6 Hz, 1H), 5.64 (dt, J = 15.1, 7.8 Hz, 1H), 4.91 (m, 1H), 4.31 (d, J = 7.8 Hz, 1H), 2.36 (dd, J = 15.1, 5.7, 1H), 2.00 (s, 3H), 1.78 (dd, J = 15.2, 6.5 Hz, 1H), 1.71 (s, 3H), 1.63 (m, 1H), 1.37 (dd, J = 13.7, 8.5 Hz, 1H), 1.13 (s, 3H), 1.12 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 165.9, 153.0, 137.5, 137.2, 129.5, 128.3, 128.0, 125.8, 125.7, 122.7, 116.5, 70.5, 67.9, 65.9, 59.3, 41.7, 37.1, 35.0, 28.9, 25.8, 21.7, 20.5, 13.1; ESI-HRMS *m*/*z* calcd for $_{26}H_{31}NO_5S_2Na$ $(M + Na)^+$ 524.1541, found 524.1524.

Peridinin derivative C (3). To a solution of olefin segment **7** (22 mg, 0.044 mmol) and ylidenbutenolide segment **5** (15 mg, 0.044 mmol) in THF (0.65 mL) was added dropwise sodium bis(trimethylsilyl)amide (1.0M in THF, 0.13 mL, 0.13 mmol) at –78 °C in the dark. After being stirred for 5 min at the same temperature, the reaction mixture was poured into water and then extracted with diethyl ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by short silica gel column chromatography (from 30% to 50% ethyl acetate in hexane) in the dark afforded peridinin derivative **3** (11 mg, 40%) as a mixture of the isomers as a red film. A solution of a mixture of all-*trans*-peridinin derivative **3** and its *cis*-isomer in benzene was left at room temperature under the fluorescence light. After 2 days, partial separation by preparative HPLC [column: Develosil CN-UG (0.6 × 25 cm); mobile phase: acetone/*n*-hexane = 1/10; flow rate: 2.0 mL/min; UVdetect: 450 nm; retention time: (all-*trans*-isomer) 49 min, (15-*cis*-isomer) 43 min] in the dark, and HPLC [column: YMC Carotenoid C30 (10 × 250 mm); reverse phase: acetonitrile/methanol/water = 87/10/3; flow rate: 2.0 mL/min.; UVdetect: 450 nm; retention time: (all-*trans*-isomer) 30 min, (15-*cis*-isomer) 24 min] in the dark, afforded the desired optically active peridinin derivative **3** as a red film: IR (neat, cm^{-1}) 3327, 2924, 1741, 1712, 1462, 1377, 1259, 1153, 1028; ^1H NMR (C_6D_6, 750 MHz) δ 7.57 (d, J = 15.5 Hz, 1H), 6.68 (d, J = 15.4 Hz, 1H), 6.62 (dd, J = 14.0, 12.3 Hz, 1H), 6.56 (d, J = 15.5 Hz, 1H), 6.45 (dd, J = 14.1, 11.9 Hz, 1H), 6.38 (dd, J = 14.3, 11.2 Hz, 1H), 6.33 (d, J = 11.7 Hz, 1H), 6.26 (dd, J = 14.2, 11.3 Hz, 1H), 6.17 (d, J = 11.7 Hz, 1H), 6.15 (s, 1H), 5.92 (d, J = 15.5 Hz, 1H), 5.20 (s, 1H), 5.19 (m, 1H), 3.86 (m, 1H), 2.35 (dd, J = 14.7, 5.3 Hz, 1H), 2.19 (ddd, J = 14.7, 5.1, 1.1 Hz, 1H), 2.13 (s, 3H), 1.79 (s, 3H), 1.72 (s, 3H), 1.71 (m, 1H), 1.62 (dd, J = 14.8, 7.2 Hz, 1H), 1.42 (m, 2H), 1.35 (m, 1H), 1.13 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 1.05 (m, 1H); ^{13}C NMR (C_6D_6,

188 MHz) δ 169.3, 168.3, 147.5, 138.1, 137.7, 137.1, 136.4, 135.8, 134.7, 134.6, 134.4, 132.5, 131.4, 129.9, 125.1, 125.0, 122.4, 118.5, 70.5, 70.3, 67.7, 67.5, 65.8, 63.9, 47.3, 42.2, 41.2, 37.3, 35.3, 35.1, 29.5, 28.8, 25.7, 25.3, 21.0, 19.9, 15.6, 12.9; ESI-HRMS *m/z* calcd for $C_{39}H_{48}O_7Na$ $(M + Na)^+$ 651.3298, found 651.3276.

(4*S*)-4-Hydroxy-2,6,6-trimethylcyclohex-1-enyltrifluoromethanesulfonate (10a). To a solution of **10** (200 mg, 0.50 mmol) in THF (2.47 mL) was added tetra-*n*-butylammonium fluoride (1.0M in THF, 1.49 mL, 1.49 mmol) at room temperature. After being stirred for 45 min at the same temperature, the reaction mixture was poured into a saturated aqueous NH_4Cl solution and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by silica gel column chromatography (from 10% to 50% ethyl acetate in hexane) afforded alcohol **10a** (112 mg, 78%) as a colorless oil: $[\alpha]^{23.0}_D$ −25.4 (c 0.99, $CHCl_3$); IR (neat, cm^{-1}) 3359, 2932, 2361, 1686, 1404, 1210, 1067, 913; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.11 (m, 1H), 2.50 (ddd, J = 17.0, 5.5, 1.9 Hz, 1H), 2.18 (ddd, J = 16.5, 9.2, 0.9 Hz, 1H), 1.86 (ddd, J = 12.4, 3.7, 0.3 Hz, 1H), 1.77 (s, 3H), 1.68 (dd, J = 11.9, 11.9 Hz, 1H), 1.22 (s, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.3, 123.9, 64.1, 49.0, 41.3, 37.1, 27.7, 27.0, 17.9; FAB-HRMS *m/z* calcd for $C_{39}H_{51}O_7Na$ $(M + H)^+$ 288.0716, found 289.0759.

***trans*-2-[(4*S*)-4-Hydroxy-2,6,6-trimethylcyclohexene]-1-(tributylstannyl)ethylene (27).** To a solution of alcohol **10a** (388 mg, 1.17 mmol) and bisstannane **26** (855 mg, 1.41 mmol) in DMF (5.86 mL) was added diisopropylethylamine (0.61 mL, 3.52 mmol), tetrakis(triphenylphosphine)palladium (67 mg, 0.059 mmol), and lithium chloride (99 mg, 2.34 mmol) After being stirred for 1 h at 90 °C, the reaction mixture was poured into water and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by silica gel column chromatography (from 0% to 30% ethyl acetate 3% triethylamine in hexane) afforded **27** (451 mg, 85%) as a colorless oil: $[\alpha]^{23.0}_D$ −72.0 (c 0.84, $CHCl_3$); IR (neat, cm^{-1}) 3360, 2924, 2855, 2361, 1579, 1464, 1174, 1045, 691; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.30 (d, J = 19.6 Hz, 1H), 5.90 (d, J = 19.2 Hz, 1H), 3.98 (m, 1H), 2.35 (dd, J = 16.5, 5.5 Hz, 1H), 2.00 (dd, J = 16.1, 9.5 Hz, 1H), 1.75 (ddd, J = 19.0, 3.6, 2.3 Hz, 1H), 1.70 (s, 3H), 16.0–1.47 (m, 6H), 1.45 (dd, J = 12.3 Hz, 1H), 1.06 (s, 3H), 1.04 (s, 3H), 0.90 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.4, 141.5, 133.9, 124.9, 65.5, 48.6, 42.5, 36.9, 30.4, 29.6, 28.8, 27.6, 21.7, 14.1, 9.9.

***trans*-2-[(4*S*)-4-Hydroxy-2,6,6-trimethylcyclohexene]-1-iodoethylene (28).** To a solution of iodide (728 mg, 2.87 mmol), Na_2CO_3 (608 mg, 5.74 mmol) in dichloromethane (11.4 mL) was added dropwise a solution of stannane **27** (654 mg, 1.44 mmol) in dichloromethane (3 mL) at 0 °C. After stirred for 5 min at 0 °C, the mixture was poured into a saturated aqueous $Na_2S_2O_3$ solution and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by silica gel column chromatography (from 5% to 30% ethyl acetate in hexane) afforded iodide **28** (379 mg, 94%) as a colorless oil: $[\alpha]^{23.0}_D$ −115.0 (c 0.64, $CHCl_3$); IR (neat, cm^{-1}) 3301, 2955, 1590, 1466, 1364, 1166, 1047, 945, 781; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.89 (d, J = 14.6 Hz, 1H), 5.96 (d, J = 14.6 Hz, 1H), 3.95 (m, 1H), 2.33 (dd, J = 17.0, 5.5 Hz, 1H), 1.94 (ddd, J = 17.0, 9.6, 1.4 Hz, 1H), 1.73 (ddd, J = 12.4, 3.7, 1.4 Hz, 1H), 1.66 (s, 3H), 1.42 (dd, J = 11.9, 11.9 Hz, 1H), 1.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.5, 139.0, 128.2, 79.5, 65.1, 48.2, 42.4, 36.8, 30.2, 28.7, 21.7; FAB-HRMS *m/z* calcd for $C_{11}H_{17}IO_7$ $(M + H)^+$ 293.0397, found 293.0423.

***trans*-2-[(4*S*)-4-Acetoxy-2,6,6-trimethylcyclohexene]-1-iodoethylene (29).** To a solution of iodide **28** (379 mg, 1.30 mmol) in pyridine (5.19 mL) was added acetic anhydride (0.24 mL, 2.59 mmol) at room temperature, and the reaction mixture was stirred for 16 h at the same temperature. A saturated aqueous $CuSO_4$ solution was added and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by silica gel column chromatography (30% ethyl acetate in hexane) afforded acetate **29** (374 mg, 86%) as a colorless oil: $[\alpha]^{25.0}_D$ −99.8 (c 1.10, $CHCl_3$); IR (neat, cm^{-1}) 2963, 2867, 1740, 1588, 1466, 1242, 1117, 1035, 968; NMR ($CDCl_3$, 400 MHz) δ 6.91 (d, J = 14.6 Hz, 1H), 6.00 (d, J = 15.1 Hz, 1H), 5.02 (m, 1H), 2.39 (dd, J = 16.9, 5.4 Hz, 1H), 2.04 (s, 3H), 2.01 (m, 1H), 1.76 (ddd, J = 11.9, 3.2, 1.8 Hz, 1H), 1.67 (s, 3H), 1.55 (dd, J = 11.5, 11.5 Hz, 1H), 1.07 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 143.3, 139.2, 127.8, 79.8, 68.3, 43.9, 38.4, 36.4, 30.0, 28.5, 21.8, 21.6; FAB-HRMS *m/z* calcd for $C_{39}H_{51}O_7$ $(M + H)^+$ 335.0502, found 335.0541.

(2*E*,4*E*,6*E*)-7-[(4′*S*)-4′-Acetoxy-2′,6′,6′-trimethylcyclohexene]-5-methylhepta-2,4,6-trien-1-ol (30). To a solution of acetate **29** (194 mg, 0.58 mmol) and (2*E*,4*E*)-5-(tributylstannyl)hexa-2,4-dien-1-ol **23** (247 mg, 0.64 mmol) in DMF (2.9 mL) was added diisopropylethylamine (0.30 mL, 1.74 mmol), bis(acetonitrile)dichloropalladium(II) (7 mg, 0.03 mmol) and lithium chloride (49 mg, 1.16 mmol). After being stirred for 50 min at room temperature, the reaction mixture was poured into water and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) afforded **30** (151 mg, 85%) as a yellow oil: $[\alpha]^{23.0}_D$ −91.0 (c 1.33, $CHCl_3$); IR (neat, cm^{-1}) 3414, 2961, 2924, 1736, 1366, 1244, 1030; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.63 (dd, J = 15.1, 11.2 Hz, 1H), 6.13–5.96 (m, 3H), 5.88 (td, J = 12.1, 5.9 Hz, 1H), 5.06 (m, 1H), 4.24 (m, 1H), 2.44 (dd, J = 17.0, 5.72 Hz, 1H), 2.06 (m, 1H), 2.05 (s, 3H), 1.92 (s, 3H), 1.77 (ddd, J = 12.2, 3.4, 1.8 Hz, 1H), 1.71 (s, 3H), 1.56 (m, 1H), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 138.3, 137.7, 135.9, 132.0, 129.3, 127.9, 125.8, 125.6, 68.4, 63.7, 43.9, 38.4, 36.6, 29.9, 28.4, 21.5, 21.4, 12.6; ESI-HRMS *m/z* calcd for $C_{19}H_{28}O_3Na$ $(M + Na)^+$ 327.1936, found 327.1940.

2-(((2′*E*,4′*E*,6′*E*)-7′-((4″*S*)-4″-Acetoxy-1″,2″-epoxy-2″,6″,6″-trimethylcyclohexene)-5′-methylhepta-2,4,6-triene)sulfanyl)benzothiazole (30a). To a solution of alcohol **30** (110 mg, 0.29 mmol), 2-mercaptobenzothiazole (68 mg, 0.41 mmol) and triphenylphosphine (107 mg, 0.41 mmol) in THF (3 mL) was added dropwise diisopropyl azodicarboxylate (0.09 mL, 0.47 mmol) at 0 °C. The reaction mixture was stirred for 10 min at room temperature and the solvents were removed *in vacuo.* To the residue was added diethyl ether and the precipitate was removed by filtration through a pad of Celite to give the crude products as a solution,

which was concentrated *in vacuo.* Purification by short silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) afforded thioether **30a** (111 mg, 84%): $[\alpha]^{23.0}_{D}$ –64.1 (c 0.93, $CHCl_3$); IR (neat, cm^{-1}) 2963, 2926, 1734, 1460, 1427, 1363, 1244, 1030; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.87 (m, 1H), 7.75 (m, 1H), 7.41 (m, 1H), 7.27 (m, 1H), 6.74 (dd, J = 14.6, 11.2 Hz, 1H), 6.09–6.04 (m, 2H), 6.02 (d, J = 10.0 Hz, 1H), 5.88 (m, 1H), 5.04 (m, 1H), 4.11 (d, J = 7.6 Hz, 2H), 2.43 (dd, J = 17.0, 5.5 Hz, 1H), 2.08 (dd, J = 17.0, 9.4 Hz, 1H), 2.04 (s, 3H), 1.91 (s, 3H), 1.73 (m, 1H), 1.69 (s, 3H), 1.56 (m, 1H), 1.08 (s, 3H), 1.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 166.2, 153.2, 138.2, 137.6, 136.3, 135.3, 131.2, 128.9, 126.7, 126.1, 125.9, 125.6, 124.2, 121.5, 120.9, 68.2, 43.9, 38.3, 36.6, 36.2, 29.9, 28.4, 21.4, 21.4, 12.56; ESI-HRMS m/z calcd for $C_{26}H_{31}NO_2S_2Na$ $(M + Na)^+$ 476.1694, found 476.1696.

2-(((2′*E*,4′*E*,6′*E*)-7′-((4″*S*)-4″-Acetoxy-2″,6″,6″-trimethylcyclohexene)-5′-methylhepta-2,4,6-triene)sulfonyl)benzothiazole (8). To a solution of the thioether **30a** (205 mg, 0.45 mmol) in ethanol (9.0 mL) was added dropwise a solution of sodium tungstate(VI) dihydrate (164 mg, 0.50 mmol) in hydrogen peroxide (30 wt.% in water, 5,42 mL) at 0 °C. After being stirred for 50 min at room temperature, the reaction mixture was poured into water and then extracted with diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by short silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) afforded the sulfone **8** (68 mg, 31%): $[\alpha]^{23.0}_{D}$ –43.5 (c 1.50, $CHCl_3$); IR (neat, cm^{-1}) 2963, 1728, 1630, 1471, 1364, 1330, 1244, 1148, 1026, 970; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.24 (m, 1H), 7.99 (m, 1H), 7.63 (m, 2H), 6.60 (dd, J = 14.9, 11.3 Hz, 1H), 6.10 (d, J = 16.2 Hz, 1H), 5.99 (d, J = 16.3 Hz, 1H), 5.98 (d, J = 11.4 Hz, 1H), 5.62 (m, 1H), 5.04 (m, 1H), 4.33 (d, J = 7.4 Hz, 2H), 2.37 (m, 1H), 2.09 (m, 1H), 2.04 (s, 3H), 1.80–1.65 (m, 1H), 1.74 (s, 3H), 1.60–1.50 (m, 1H), 1.43 (s, 3H), 0.97 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 166.3, 153.3, 139.2, 138.5, 137.8, 137.6, 133.9, 129.5, 128.6, 128.3, 128.2, 127.6, 126.1, 123.0, 116.1, 69.2, 59.8, 44.7, 38.7, 37.8, 29.5, 28.9, 22.12, 20.8, 13.2; ESI-HRMS m/z calcd for $C_{26}H_{31}NO_4S_2Na$ $(M + Na)^+$ 508.1592, found 508.1547.

Peridinin derivative D (4). To a solution of sulfone **8** (22 mg, 0.045 mmol) and aldehyde **5** (16 mg, 0.045 mmol) in THF (0.68 mL) was added dropwise sodium bis(trimethylsilyl)amide (1.0M in THF, 0.14 mL, 0.14 mmol) at –78 °C in the dark. After being stirred for 5 min at the same temperature, the reaction mixture was poured into water and then extracted with diethyl ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by short silica gel column chromatography (from 30% to 50% ethyl acetate in hexane) in the dark afforded peridinin derivative **4** (13 mg, 47%) as a mixture of the isomers as a red film. A solution of a mixture of all-*trans*-peridinin derivative **4** and its isomer in benzene was left at room temperature under fluorescent light. After 4 days, partial separation by preparative HPLC [column: Develosil CN-UG (0.6 × 25 cm); mobile phase: acetone/*n*-hexane = 1/10; flow rate: 2 mL/min; UVdetect: 459 nm; retention time: (all-*trans*-isomer) 68 min, (15-*cis*-isomer) 61 min] in the dark, and HPLC [column: YMC Carotenoid C30 (10 × 250 mm); reverse phase: acetonitrile/methanol/water = 87/10/3; flow rate: 2.0 mL/min; UVdetect: 459 nm; retention time: (all-*trans*-isomer) 34 min] in the dark afforded the desired optically active peridinin derivative **4** as a red film: IR (neat, cm^{-1}) 3449, 2924, 2853, 2363, 1751, 1655, 1509, 1364, 1242, 1124, 1034; ^1H NMR (C_6D_6, 750 MHz) δ 7.57 (d, J = 15.5 Hz, 1H), 6.68 (dd, J = 13.7, 12.3 Hz, 1H), 6.57 (d, J = 15.5 Hz, 1H), 6.49 (dd, J = 14.1, 12.0 Hz, 1H), 6.42 (dd, J = 14.1, 12.0 Hz, 1H), 6.36 (d, J = 11.4 Hz, 1H), 6.34 (dd, J = 14.1, 11.0 Hz, 1H), 6.27 (d, J = 15.8 Hz, 1H), 6.26 (d, J = 11.4 Hz, 1H), 6.19 (d, J = 16.1 Hz, 1H), 6.17 (s, 1H), 5.29 (m, 1H), 5.22 (s, 1H), 3.76 (m, 1H), 2.46 (dd, J = 17.1, 5.9 Hz, 1H), 2.20 (ddd, J = 14.2, 4.8, 1.0 Hz, 1H), 2.15 (s, 3H), 2.13 (m, 1H), 1.87 (m, 1H), 1.84 (s, 3H), 1.68 (s, 3H), 1.64 (dd, J = 11.9, 11.9 Hz, 1H), 1.42 (m, 2H), 1.13 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 1.07 (s, 3H), 1.06 (m, 1.16); ^{13}C NMR (C_6D_6, 188 MHz) δ 169.8, 168.3, 147.4, 139.0, 138.1, 137.7, 137.2, 136.3, 134.6, 134.3, 134.1, 131.6, 129.6, 126.7, 126.4, 125.1, 122.4, 118.5, 70.4, 68.1, 67.4, 63.8, 47.3, 44.4, 41.2, 38.8, 36.8, 35.3, 30.1, 29.5, 28.6, 25.3, 21.5, 21.0, 19.9, 15.6, 12.7; ESI-HRMS m/z calcd for $C_{39}H_{50}O_6Na$ $(M + Na)^+$ 637.3505, found 637.3517.

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