Stereocontrolled Total Synthesis of a Polyfunctional Carotenoid, Peridinin

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Peridinin, which was isolated from the planktonic algae dinoflagellates causing red tides, is a highly oxidized carotenoid containing an allene and a characteristic (*Z*)-γ-ylidenebutenolide function in the main conjugated polyene chain in addition to functionalized cyclohexane rings at both ends of the molecule. We achieved a stereocontrolled total synthesis of peridinin by featuring the Sharpless asymmetric epoxidation under precise reaction conditions, Wittig reaction with silylfuranmethylide followed by photosensitized oxygenation, stereocontrolled Pd-catalyzed one-pot (*Z*)-γ-ylidenebutenolide synthesis, and modified Julia−Kocienski olefination. This synthesis is the first example of controlling the stereochemistry of polyfunctional allenic carotenoids.

Introduction

More than 600 carotenoids have been found in nature as brilliant yellow-to-red pigments and auxiliary light-harvesting pigments for photosynthesis. Among them, some carotenoids possess several oxy-functional groups in addition to the long conjugated polyene system including allenic or acetylenic groups.[1] During the past 15 years, various efforts have been made to achieve the syntheses of optically active polyfunctional allenic carotenoids, for example, peridinin (**1**),[2] fucoxanthin,[3] neoxanthin,[4] mimulaxanthin,[5] and paracentrone[6] (Figure 1).[7] However, satisfactory control of the stereochemistry in the synthesis of these carotenoids has not been achieved, and this problem has hitherto remained unsolved. We have therefore developed a new strategy for the efficient synthesis of polyfunctional carotenoids represented by peridinin, which is one of the most architecturally complex molecules among the carotenoids.

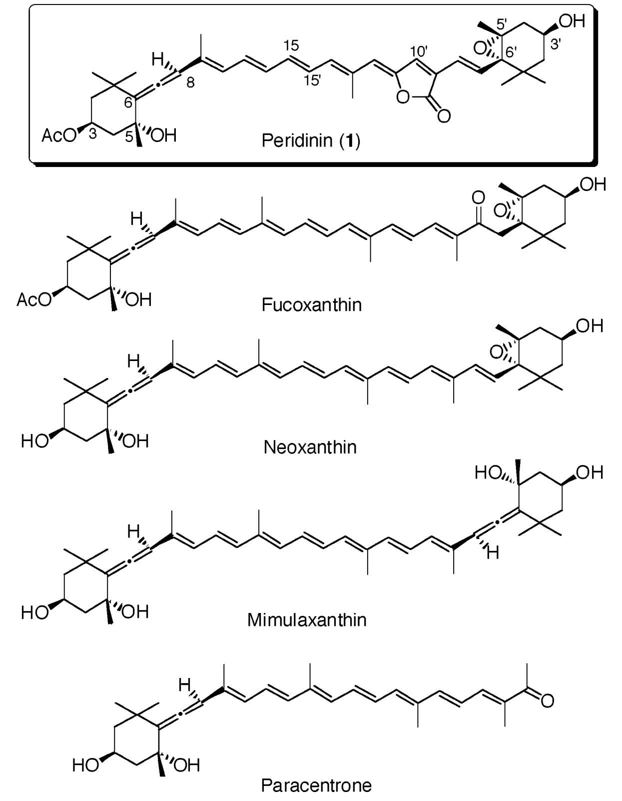

FIGURE 1. Naturally occurring allenic carotenoids.

Peridinin was first isolated from the planktonic algae dinoflagellates causing red tides in 1890;[8] later, this

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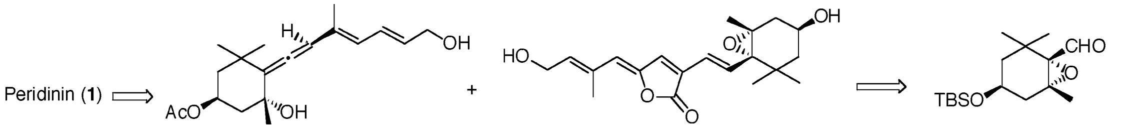
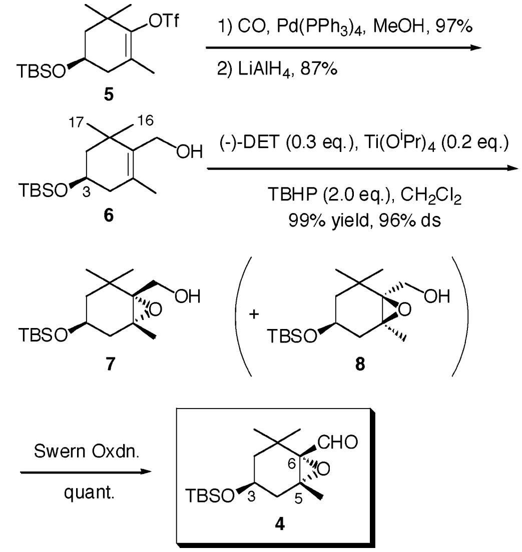


C_{17}-Allenic Half-Segment **2** C_{20}-Ylidenebutenolide Half-Segment **3** the Common Epoxyaldehyde **4**

FIGURE 2. Retrosynthetic analysis.

SCHEME 1



molecule was found in several marine sources as the main carotenoid responsible for photosynthesis in the sea.[9] Its antitumor and anticarcinogenic activities have been reported.[10] The structure and absolute stereochemistry of peridinin was determined by Liaaen-Jensen and co-workers by chemical derivation, the fragmentation pattern of MS, and CD spectra in 1980.[11] Peridinin (**1**) is a highly oxidized C_{37}-*nor*-carotenoid possessing an allene and a characteristic (*Z*)-γ-ylidenebutenolide moiety within the conjugated polyene chain, in addition to functionalized cyclohexane rings at both ends of the molecule.[12] The synthesis of **1** was reported by Ito and co-workers in 1990, 100 years after its first isolation, and the structure of this historic carotenoid was confirmed.[2] In their synthesis, however, control of the stereochemistry at the terminal cyclohexane rings, conjugated polyene chain, and the (*Z*)-γ-ylidenebutenolide moiety was not considered and hence the yield was very poor, although they found an efficient one-pot procedure for the construction of the conjugated γ-ylidenebutenolide moiety.

Herein, we report our investigation toward the total synthesis of peridinin, featuring stereochemical control of the six asymmetric carbons and the geometry of the seven double bonds in the molecule, which leads to the development of a new synthetic strategy for polyfunctional carotenoids.[13]

Results and Discussion

Retrosynthetic Analysis. The challenges involved in the stereocontrolled synthesis of peridinin (**1**) are summarized as follows: (1) the stereocontrolled construction of the oxygen functionality at the terminal cyclohexane rings and (2) the stereocontrolled construction of the all-trans-conjugated polyene chain containing the asymmetric allenic function and the (*Z*)-γ-ylidenebutenolide moiety. Keeping these issues in mind, we bisected this molecule at the central C-15 and C-15′ bond (Figure 1). The molecule was divided into two advanced segments; the C_{17}-allenic segment **2** and the C_{20}-ylidenebutenolide segment **3** (Figure 2). An optically active epoxyaldehyde derivative **4** was chosen as a common intermediate for the synthesis of both segments.

Stereocontrolled Preparation of the Common Intermediate, Epoxyaldehyde 4. In the carotenoid synthesis, complete stereocontrol of the asymmetric carbons at the C-3, C-5, and C-6 positions of the terminal cyclohexane ring had not been achieved (Figure 1); in the previously reported synthesis, the ratio of the diastereomers was less than 7:3, and their separation was difficult.[2–6,14] Thus, the stereocontrol at these asymmetric carbons has been left unsolved.

We achieved a highly stereoselective synthesis of the epoxyaldehyde **4** by finding the precise reaction conditions of the Sharpless asymmetric epoxidation (AE)[15] on allyl alcohol **6**,[16] which was easily prepared from known enantiomerically pure vinyltriflate **5**[2] by Pd-catalyzed methoxycarbonylation[17] (97%) followed by LAH reduction (87%) (Scheme 1). The desired α-epoxide **7** was successfully obtained in 99% yield with 96% ds, even on a 20-g scale, by use of freshly prepared reagents and solvents

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[17] (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40*, 532. (c) Hidai, M.; Hikita, T.; Wada, Y.; Furikura, Y.; Uchida, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2075.

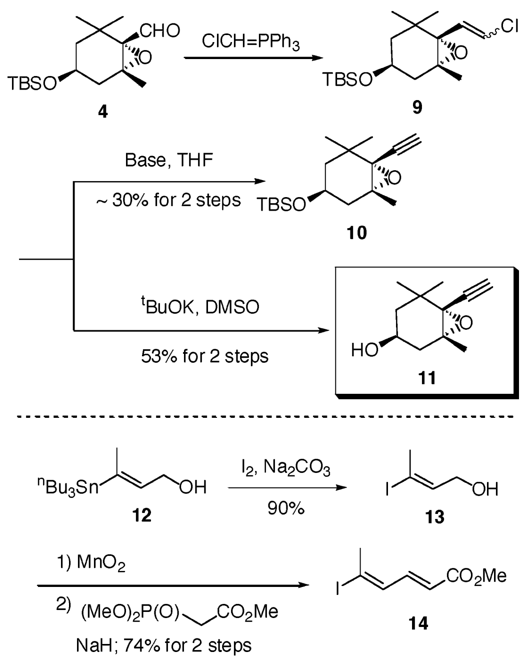
and exact amounts of the reagents [(−)-D-DET (0.3 equiv), Ti(O^{i}Pr)$_4$ (0.2 equiv), and *tert*-butylhydroperoxide (2.0 equiv)] at a constant temperature (−20 °C),[18] while the epoxidation under the reported conditions gave a 4:1 mixture of α-epoxide **7** and *β*-epoxide **8**. On the other hand, the Sharpless AE with (+)-L-DET gave the corresponding *β*-epoxide **8** with high diastereoselection (>95% ds) under the reported conditions by use of commercially available reagents and solvents without further purifications. These observations led us to the conclusion that the Sharpless AE of **6** with (−)-D-DET would be a mismatched pair at the C-3 stereochemistry.

The α-epoxide **7** was then transformed into **4** by the Swern oxidation,[19] and sufficient quantities of the common intermediate, epoxyaldehyde **4**, were prepared in four steps and 84% overall yield from the known **5**. This is the first example achieving satisfactory control of the stereochemistry between the C-3 hydroxy group and the C-5,6 epoxide at the terminal cyclohexane ring in carotenoid synthesis.

Stereocontrolled Synthesis of the Allenic Half-Segment 2. The chiral allenic moiety of carotenoids is usually attached at the terminal cyclohexane ring in an exo manner, and at the allylic position of this ring, the hydroxy groups that possesses syn and anti configurations with respect to the allenic vinyl hydrogen and the C-3 acetoxy group, respectively, are present. As the only practical method for the preparation of this characteristic allylhydroxyallenic moiety, stereospecific S$_N$2′ reduction of a conjugated ethynylepoxide such as **15** with DIBAL has been confirmed.[2–6,20] Therefore, the stereocontrolled preparation of **15** was required (Scheme 3). We applied the Sharpless asymmetric epoxidation under our precise reaction conditions described above and a Pd-catalyzed sp−sp^2 cross-coupling reaction. The Pd-catalyzed sp−sp^2 and sp^2−sp^2 cross-coupling is an effective method for the stereocontrolled construction of the conjugated polyene,[22] which is the essential problem in carotenoid synthesis.[23]

The carbon chain extension from **4** by the Wittig reaction gave vinyl chloride **9** as a stereoisomeric mixture, which was transformed into an acetylene derivative **10** by treatment with a base in tetrahydrofuran (THF) in a moderate yield (Scheme 2). Interestingly, under *t*BuOK/dimethyl sulfoxide (DMSO) conditions, the TBS protecting group was simultaneously removed to give the C-3-hydroxyepoxyacetylene **11**[14] in 53% yield for the two steps after crystallization. Meanwhile, vinyl iodide **14**, which is a component of the allenic segment **2** (Scheme 3), was prepared by the sequence of a tin−halogen exchange of (*E*)-vinyl stannane **12**[24] leading to **13**,[25] oxidation, and then the Horner−Emmons reaction of the resulting aldehyde.[26]

SCHEME 2



The Sonogashira cross-coupling reaction[27] between **11** and **14** in the presence of Pd(PPh$_3$)$_4$, cuprous iodide, and triethylamine in THF afforded the desired coupling product **15** in 60% yield, with complete stereochemical control (Scheme 3). Furthermore, use of diisopropylamine as a solvent improved the yield up to 84%. The conjugated ethynylepoxide **15** obtained was transformed into allenic triol **16**[28] by the stereospecific hydride reduction in 80% yield. An acetyl group was introduced into the secondary hydroxyl group of **16** by a sequence of MnO$_2$ oxidation and acetylation[28] and followed by reduction to produce the acetate **2** in excellent yield over the three steps. In this manner, the allenic half-segment **2** was efficiently prepared in a stereocontrolled way in seven steps and in 30% overall yield from the common intermediate **4**.

First-Generation Synthesis of the Ylidenebutenolide Half-Segment 3: Retrosynthetic Analysis. The most challenging aspect of peridinin synthesis was the stereocontrolled preparation of a characteristic conjugated (*Z*)-*γ*-ylidenebutenolide function. Lu et al.[29] re-

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[19] (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Tidwell, T. T. *Synthesis* **1990**, 857. (c) Tidwell, T. T. *Org. React.* **1991**, *39*, 297.

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[23] For an application of the Pd-catalyzed coupling reaction to the carotenoid synthesis, see (a) Zeng, F.; Negishi, E. *Org. Lett.* **2001**, *3*, 719. (b) Vaz, B.; Alvarez, R.; de Lera, A. R. *J. Org. Chem.* **2002**, *67*, 5040.

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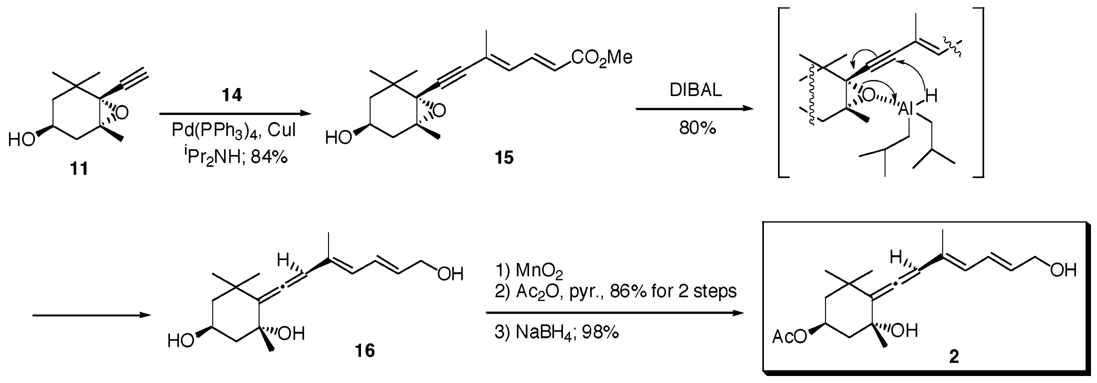
SCHEME 3



ported the stereoselective construction of (Z)-γ-ylidenebutenolide by utilizing the Pd(II)-catalyzed intramolecular 5-exo cyclization of (Z)-2-en-4-ynoic acid. This method was further developed for the synthesis of natural products containing the γ-ylidenebutenolide moiety by Negishi's group[30] and that of Rossi.[31] In our preliminary study toward the total synthesis of peridinin, we independently achieved the synthesis of a conjugated butenolide-containing sesquiterpene, freelingyne, by utilizing the stereocontrolled Pd(II)-catalyzed intramolecular lactonization.[32]

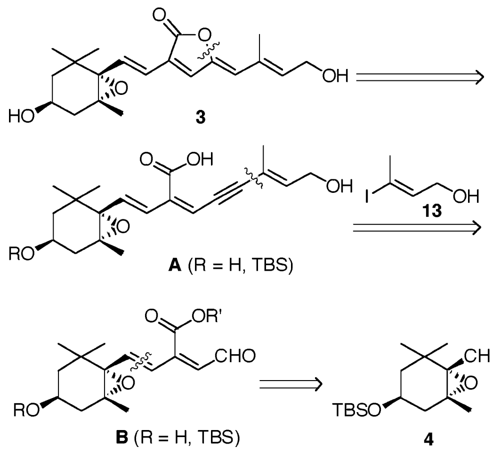
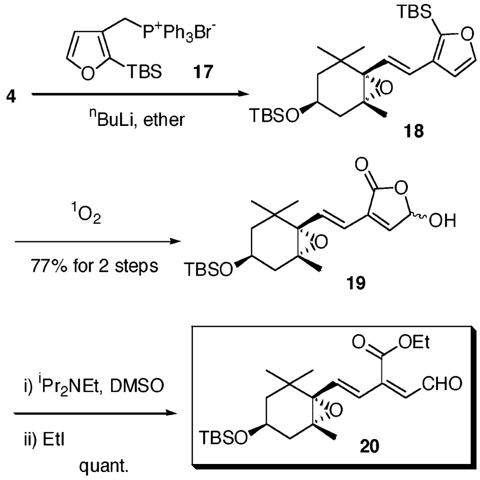


FIGURE 3. First-generation synthetic strategy for the ylidenebutenolide segment **3**.

On the basis of previous results, a conjugated ethynylcarboxylic acid **A** was selected as the synthetic precursor of ylidenebutenolide **3**, which should be obtained from (Z)-β-alkoxycarbonyldienal **B** via the Sonogashira coupling with **13** (Figure 3). The challenge was, therefore, how to synthesize the dienal **B** from the common intermediate **4** in a stereocontrolled manner. We finally achieved this aim by utilizing the silylfuran chemistry developed in our laboratory.[33–35]

SCHEME 4



Effective Construction of the β-Alkoxycarbonyldienal System. The Wittig reaction of the common intermediate **4** with our silylfuran–Wittig reagent **17**[34] proceeded very smoothly to give the conjugated furan derivative **18** as a single stereoisomer (Scheme 4). Notably, other attempts to extend the carbon chain from **4** by alkyllithium, the Grignard reagent, and the Julia reagent were unsuccessful.

The silylfuran moiety of **18** was chemoselectively oxidized with ${}^1O_2$[33a] to regiospecifically afford the corre-

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[30] Review: Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707. See also: (a) Kotora, M.; Negishi, E. *Tetrahedron Lett.* **1996**, *37*, 9041. (b) Liu, F.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8591. (c) Kotora, M.; Negishi, E. *Synthesis* **1997**, 121. (d) Xu, C.; Negishi, E. *Tetrahedron Lett.* **1999**, *40*, 431. (e) Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65.

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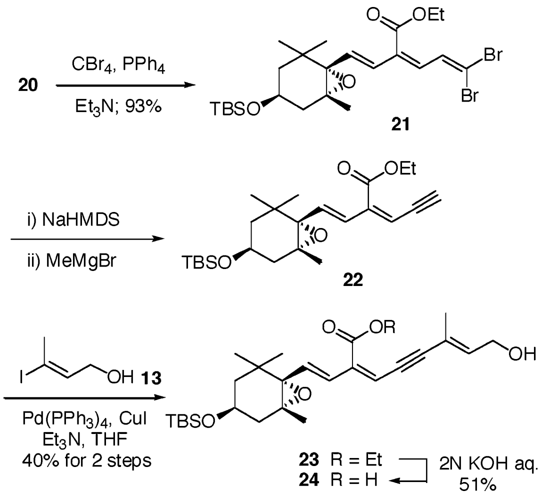
SCHEME 5



sponding γ-hydroxybutenolide **19** in 77% yield in two steps. The ring opening of the resulting γ-hydroxybutenolide **19** was then achieved without isomerization of the double bond by treatment with diisopropylethylamine and ethyl iodide in DMSO to furnish (*Z*)-β-alkoxycarbonyldienal **20**, that is, compound **B**, in excellent yield.[35]

The next step in the synthesis of **3** was the transformation of aldehyde **20** to an acetylene derivative such as **22**, which would be prepared through vinyldibromide **21**. The desired **21** was obtained in 93% yield under the Chuche-modified Corey−Fuchs conditions,[36c] by treatment of **20** with carbon tetrabromide and triphenylphosphine in the presence of triethylamine at −60 °C (Scheme 5). The subsequent transformation from **21** into **22** was troublesome; treatment with 2 equiv of *n*BuLi or LDA according to the reported procedure[36a,b] gave the expected product **22** in a very low yield. On the other hand, treatment with NaHMDS[36c] at −100 °C cleanly produced the intermediary bromoacetylene, which was successfully converted into terminal acetylene **22** by reaction with 2 equiv of MeMgBr.

The Sonogashira coupling[27] of the unstable acetylene derivative **22** with C_4-vinyl iodide **13**[25,26] proceeded smoothly to produce the corresponding coupling product **23** in 40% yield in two steps. Access to carboxylic acid **24** from ester **23** was not trivial due to the presence of the labile polyene moiety. After careful examination, the desired carboxylic acid **24**, that is, **A**, was obtained in 51% yield by treatment of **23** with 2 N aqueous KOH.

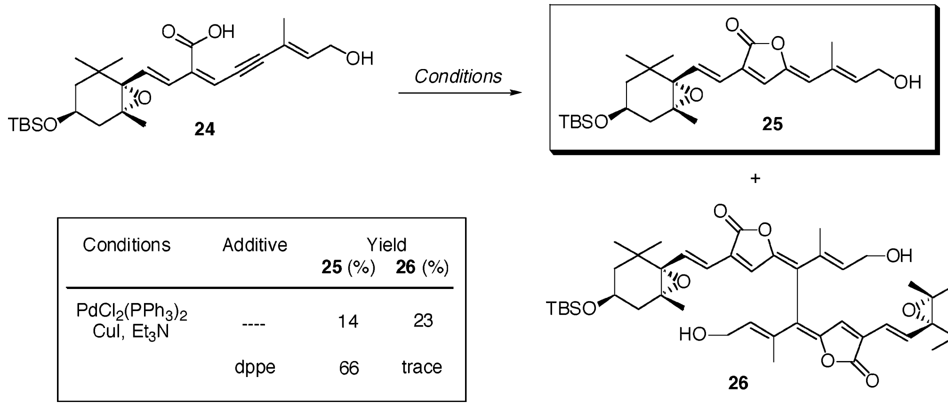
Palladium(II)-Catalyzed Intramolecular Lactonization. With the conjugated ethynylcarboxylic acid **24** in hand, the key stage was set up for the synthesis of ylidenebutenolide half-segment **25** by intramolecular lactonization. The treatment of **24** with $PdCl_2(PPh_3)_2$, cuprous iodide, and triethylamine in THF, which are conditions similar to those reported by Lu and coworkers,[26] produced the desired **25** in low yield and produced a significant amount of the dimer **26** (Scheme 6).[37] Meanwhile, the desired butenolide **25** was obtained in 66% yield as a sole stereoisomer under our previously reported conditions with the coexistence of a bidentate ligand, 1,2-bis(diphenylphosphino)ethane (dppe).[32]

The mechanism of the Pd-catalyzed lactonization could be explained as shown in Figure 4.[29,38] The initial Pd(0) species is converted to Pd(II) by oxidative addition with HX generated under the reaction conditions, and this Pd(II) species coordinated with ethynylcarboxylic acid **24** to produce the complex **i**. This is followed by 5-exo cyclization accompanied by the elimination of HX to produce an alkenylpalladium(II) complex **ii**. Reductive elimination of the intermediate **ii** afforded the desired butenolide **25** and Pd(0) species. On the other hand, the dimer **26** would be produced via **iv,** which was formed from **iii** bearing no phosphine ligands. The Pd-catalyzed lactonization in the *absence* of dppe would produce the alkenylpalladium(II) intermediate **iia**; in the *presence* of dppe, the alkenyl-Pd(II) intermediate **iib** would be formed. It is suggested that the dissociation from **ii** to **iii** would be prevented by a strong coordination of the bidentate ligand with the palladium; the formation of the dimer **26** from **iii** would be suppressed by the presence of dppe.

Thus, we achieved the completely stereocontrolled synthesis of the ylidenebutenolide **25**, but some problems remained in terms of the low yields and the relatively long reaction procedure (eight steps and 10% overall yield from the common intermediate **4**, for a first-generation synthesis).

Second-Generation Synthesis: Development of a Novel Pd-Catalyzed Domino Ylidenebutenolide Formation. To improve the overall efficiency, an allyl group, which was expected to be removed by a Pd-catalyzed reaction, was selected as a protecting group for the C-9 carboxyl moiety (Scheme 5).[39] Because the Sonogashira

SCHEME 6



Conditions	Additive	Yield	
		25 (%)	**26** (%)
$PdCl_2(PPh_3)_2$ CuI, Et_3N	----	14	23
	dppe	66	trace

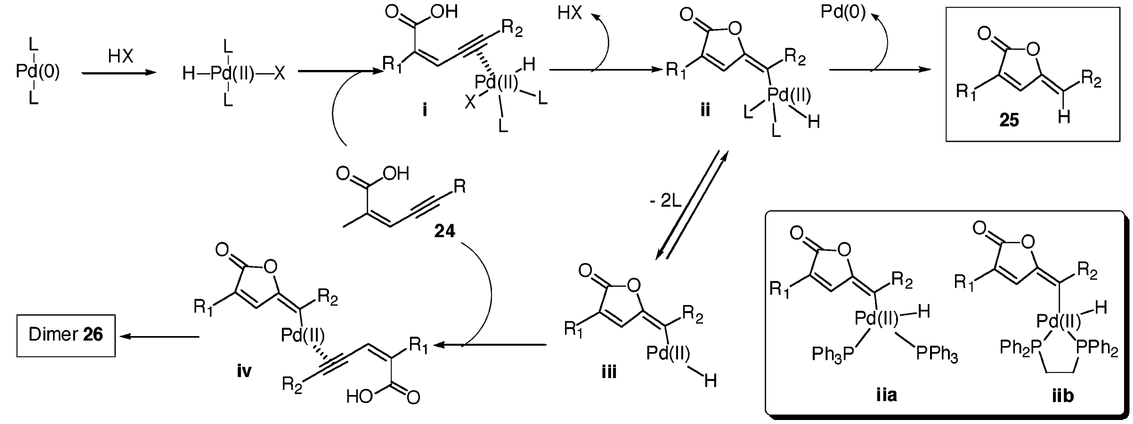
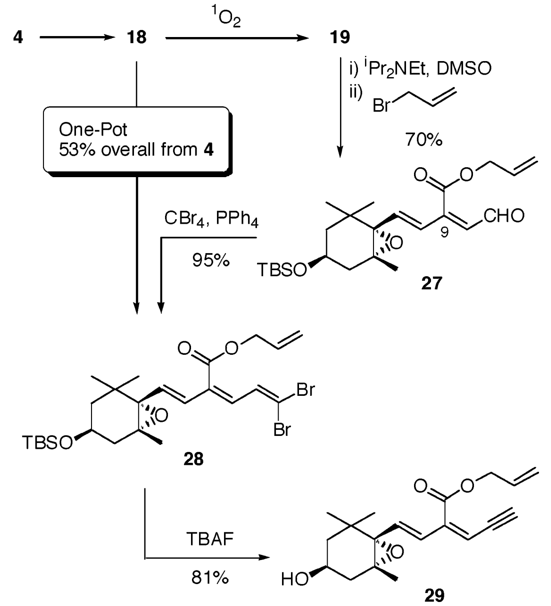
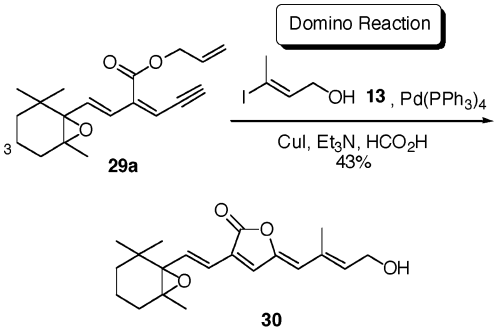


FIGURE 4. Possible mechanism for the Pd-catalyzed intramolecular lactonization.

SCHEME 7



SCHEME 8



coupling and the following lactonization also proceeded with the aid of a Pd catalyst, we envisioned that this three-step sequence would proceed in a domino fashion or in a one-pot procedure under optimized reaction conditions.

Dibromide **28** was obtained from silylfuran **18** (Scheme 4) by a similar procedure through the allyl ester **27** [$^1O_2$ oxygenation, allyl ester formation (70%), and then dibromo olefination (95%)] (Scheme 7). It is noteworthy that this sequence was efficiently realized in a one-pot procedure; the continuous addition of the respective reagents in three-step reactions in one flask gave the desired dibromide **28** as a sole stereoisomer in 53% overall yield from **4**. Furthermore, the direct conversion into the C-3-hydroxyacetylene **29** in one flask was also achieved by treatment of intermediary **28** with excess amounts of TBAF (81%). To the best of our knowledge, the transformation from a 1,1-dibromoethane derivative into the terminal acetylene by TBAF has never been obtained before,[40,41] the generality of which is now under investigation in our laboratory.

Having obtained acetylene **29**, we were ready for a domino formation of the ylidenebutenolide **3**. First, DL-3-dehydroxy congener **29a** as a model compound was examined. A mixture of **29a** and vinyl iodide **13** was stirred overnight in the presence of catalytic amounts of Pd($PPh_3)_4$, cuprous iodide, and excess amounts of formic acid in triethylamine at room temperature. The desired ylidenebutenolide **30** was obtained in 43% yield as a sole product (not optimized) (Scheme 8).

This domino reaction could be explained by considering the successive action of Pd(0) and the π-allyl-Pd(II) catalyst as shown in Figure 5. First, Pd(0) and the copper-catalyzed Sonogashira coupling of **29a** with **13** proceeded to afford **i** (path A). The coupling product **i** then produced the π-allylpalladium intermediate **ii**, which underwent the π-allylpalladium(II)-assisted regio- and stereoselective intramolecular cyclization[42] via **iii** to form the

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(37) (a) In the case of the 3-dehydroxy congener, the corresponding desired ylidenebutenolide was obtained as a single product under these conditions; see Supporting Information. (b) Experimental conditions and data for compounds **20**−**26** are described in Supporting Information.

(38) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323.

(39) Review: (a) Solomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron* **1993**, 49, 3714. (b) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1.

(40) For the transformation from 1,1-dibromoethene into bromoacetylene, see Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

(41) For the transformation from vinylbromide into acetylene by fluoride ion (TBAF, KF), see (a) Naso, F.; Ronzini, L. *J. Chem. Soc., Perkin Trans. 1* **1974**, 340. For the transformation from haloacetylene into the corresponding acetylene by halogen ion, see (b) Verplough, M. C.; Donk, L.; Bos, H. J. T.; Drenth, W. *Rec. Trav. Chim.* **1971**, *90*, 765. (c) Tanaka, R.; Zheng, S. Q.; Kawaguchi, K.; Tanaka, T. *J. Chem. Soc., Perkin Trans. 2* **1980**, *11*, 1714.

(42) Mandai, T.; Ohta, K.; Baba, N.; Kawada, M.; Tsuji, J. *Synlett* **1992**, 671.

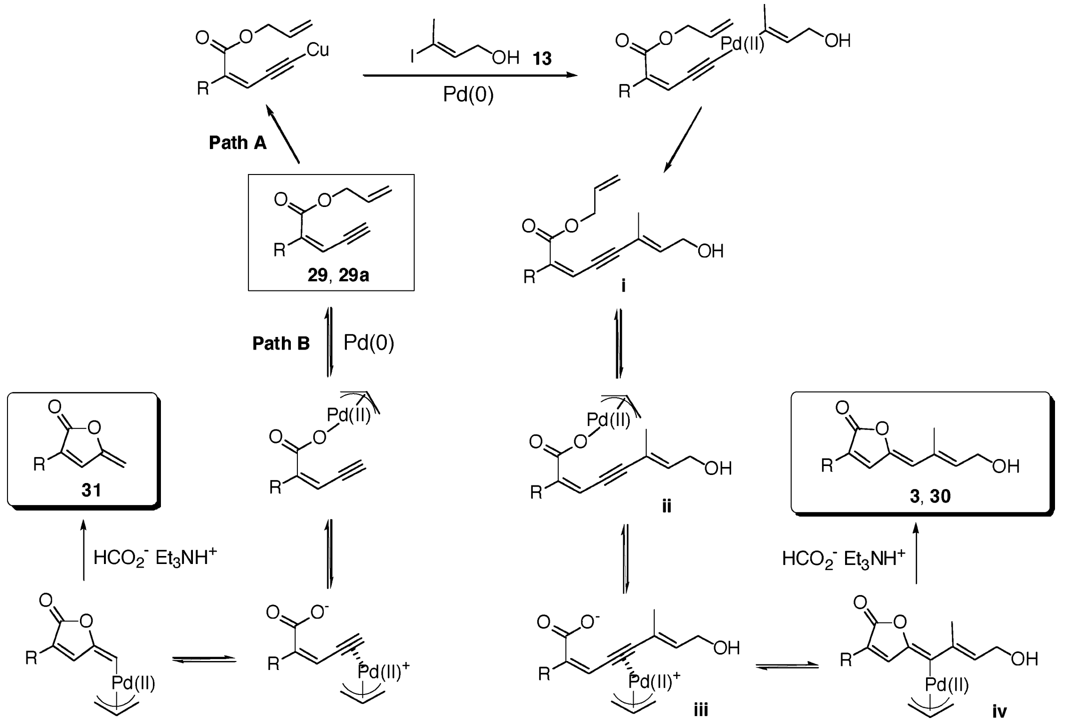
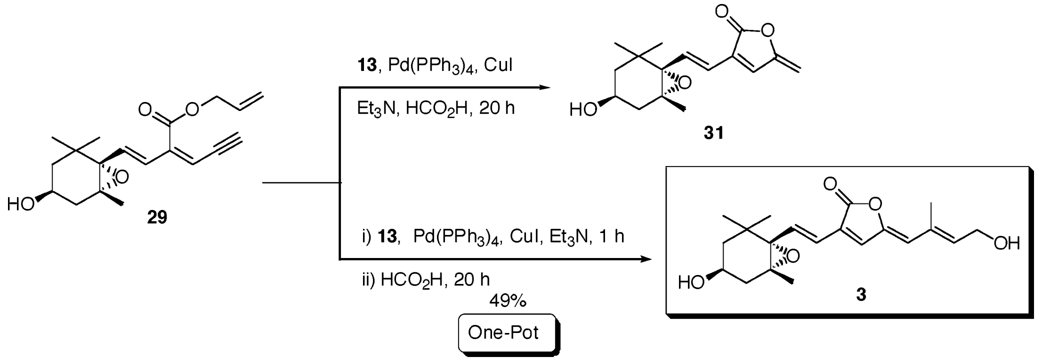


FIGURE 5. Possible mechanism for the Pd-catalyzed domino ylidenebutenolide formation reaction.

SCHEME 9



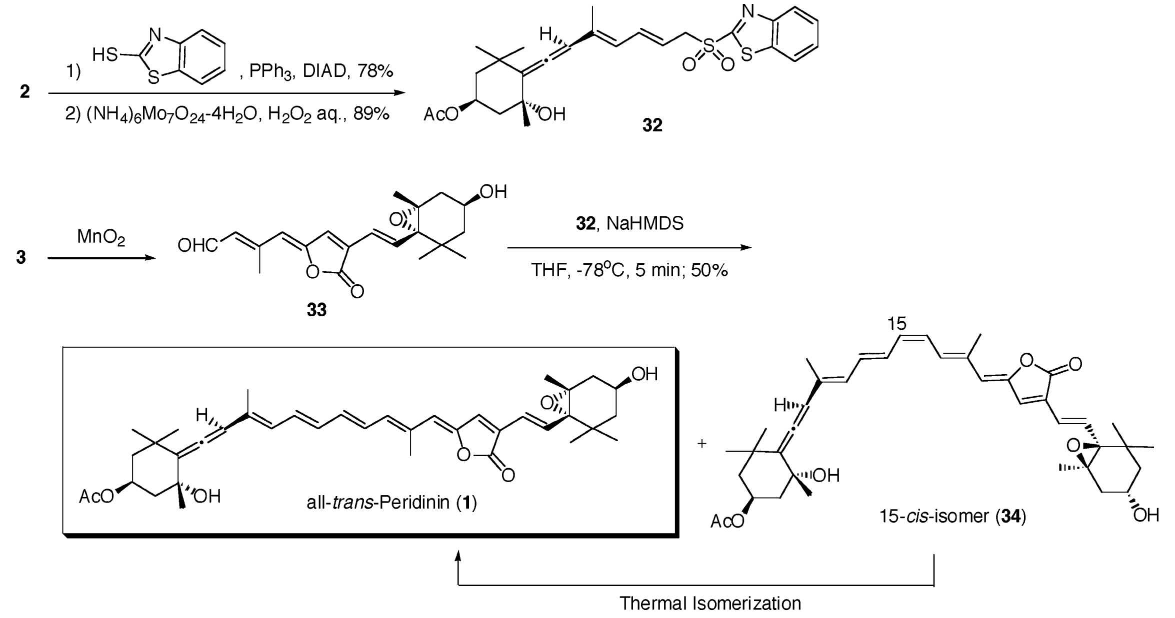
corresponding π-allylalkenylpalladium lactone intermediate **iv**. In the final step, the π-allylalkenylpalladium moiety in **iv** was removed by hydrogenolysis with triethylammonium formate to produce the desired γ-ylidenebutenolide **30**.

Encouraged by this result, we attempted to carry out the same domino procedure for the preparation of the hydroxyl derivative **3** under identical conditions. However, the reaction of **29** with vinyl iodide **13** mainly afforded γ-methylene-γ-butenolide **31** (Scheme 9). This result was probably because the π-allyl-Pd(II)-catalyzed lactonization (path B) was more favorable than the Pd(0)-catalyzed Sonogashira coupling (path A) in this case, and path B produced γ-methylene-γ-butenolide **31**, as shown in Figure 5. Interestingly, the presence of the hydroxy group at the C-3 position affected the reaction pathway. In the case of the 3-hydroxy derivative **29**, the presence of formic acid led to the formation of undesired **31**. We envisaged that the desired Sonogashira-coupling would be preferred in the absence of formic acid and that the later addition of the hydride source would afford the desired ylidenebutenolide **3**. Fortunately, this consideration brought about the successful one-pot procedure for **3**. Thus, a mixture of **29** and **13** was stirred in the presence of catalytic amounts of $Pd(PPh_3)_4$ and cuprous iodide in triethylamine at room temperature for 1 h. After the complete consumption of **29** was ascertained by TLC, formic acid was added to the reaction mixture at room temperature, and then the resulting mixture was stirred for a further 20 h. By this procedure, we obtained the desired ylidenebutenolide **3** in 49% yield as a single stereoisomer.

The efficient and stereocontrolled elaboration of the ylidenebutenolide segment **3** was thus achieved from the common intermediate **4** in *only* four steps in 21% overall yield, focusing on the sequential three one-pot reactions. This is a so-called second-generation synthesis.

Completion of the Total Synthesis by Utilizing the Modified Julia–Kocienski Olefination. With the advanced C_{17}-allenic segment **2** (Scheme 3) and the C_{20}-ylidenebutenolide segment **3** in hand, the final elaboration was conducted toward the total synthesis of peridinin (**1**) via the connection of both segments. After several trials, we noticed that the allyl halides derived from the

SCHEME 10



allenic segment **2** were unstable under the reaction conditions required for the preparation of the corresponding Wittig salt, although a very similar C_{15}-Wittig salt was reported.[3] We then turned our attention to the modified Julia–Kocienski olefination.[43] This olefination reaction seemed to be attractive for the preparation of the unstable conjugated polyene chains, because it can be carried out at low temperature. Recently, this coupling reaction has been shown to be effective for polyene macrolide synthesis.[44] On the other hand, the coupling between conjugated sulfone derivatives and the conjugated aldehydes has been less studied.[45]

Allene **2** was transformed into benzothiazolyl sulfone **32** by the Mitsunobu reaction with 2-mercaptobenzothiazole, followed by the molybdenum(VI)-catalyzed oxidation (Scheme 10). The conjunction between sulfone **32** and aldehyde **33**, which was derived from ylidenebutenolide **3** by manganese dioxide oxidation, successfully proceeded within 5 min by use of 2 equiv of NaHMDS as a base at −78 °C in the dark. The crude product obtained as a red film was a mixture of the desired *all-trans*-peridinin (**1**) and its 15-*cis* congener (**34**) in a 1:3 ratio based on ^{1}H NMR analysis (see Supporting Information). Fortunately, we found that the cis isomer (**34**) was isomerized into the thermodynamically more stable trans isomer (**1**) in a benzene solution at room temperature in the dark. Thus, after 3 days, the thermodynamic isomerization from the 15-cis isomer to the all-trans isomer reached more than a 5:1 ratio. This phenomenon was followed by the ^{1}H NMR and HPLC analyses as shown in Figure 6.

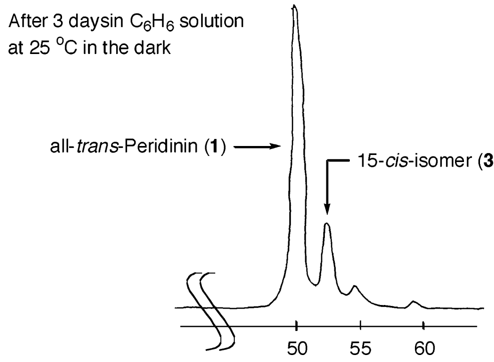


FIGURE 6. HPLC analysis after the thermal isomerization. Conditions: column, Develosil CN–UG (0.6 × 25 cm); UV detection, 450 nm; mobile phase, acetone/*n*-hexane = 1/10; flow rate, 1.54 mL/min.

The desired optically active peridinin (**1**) was obtained after purification by preparative HPLC in the dark. The spectral data for the synthesized peridinin (^{1}H and ^{13}C NMR, IR, MS, and CD spectra) were in good agreement with those for the natural product.[2,11] Thus, we completed the convergent and stereocontrolled total synthesis of the polyfunctional C_{37} *nor*-carotenoid, peridinin.

Summary

In summary, we achieved an efficient and convergent total synthesis of the polyfunctional carotenoid peridinin by controlling the stereochemistry of all six asymmetric carbons and the geometry of the seven double bonds in this molecule. Our synthesis focuses on the stereocontrolled preparation of the common intermediate **4** by

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[43] (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336. (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856. (d) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26. (d) Recent review: Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.

[44] For recent application to the natural product synthesis, see (a) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102. (b) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2002**, *124*, 2263. (c) Kang, S. H.; Jeong, J. W.; Hwang, Y. S.; Lee, S. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 5411. (d) Lee, E.; Song, H. Y.; Kang, J. W.; Kim, D. S.; Jung, C. K.; Joo, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 384. (e) Lam, H. W.; Pattenden, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 508. (f) Compostella, F.; Franchini, L.; Panza, L.; Prosperi, D.; Ronchetti, F. *Tetrahedron* **2002**, *58*, 4425. (g) Lausten, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879.

[45] Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285.

utilizing Sharpless asymmetric epoxidation under restrictedly optimized conditions, the stereocontrolled construction of the conjugated polyene moiety including (*Z*)-γ-ylidenebutenolide by Pd-catalyzed reactions, and a modified Julia−Kocienski olefination. In particular, the construction of the characteristic conjugated (*Z*)-γ-ylidenebutenolide moiety was achieved in a one-pot procedure utilizing Pd(0)- and Pd(II)-catalyzed reactions.

We believe that this is the first example of controlling the stereochemistry of polyfunctional allenic carotenoids and that the methodology developed here will be applicable to other carotenoid synthesis.

Experimental Section

Methyl (2*E*,4*E*)-7-[(1′*R*,2′*R*,4′*S*)-1′,2′-Epoxy-4′-hydroxy-2′,6′,6′-trimethylcyclohexyl]-5-methylhepta-2,4-dien-6-ynoate (15). To a solution of **11**[14] (2.15 g, 11.9 mmol) and **14**[26] (3.00 g, 11.9 mmol) in diisopropylamine (60 mL) were added tetrakis(triphenylphosphine)palladium (138 mg, 0.12 mmol) and cuprous iodide (22.5 mg, 0.12 mmol) at room temperature. After being stirred for 1 h at the same temperature, the reaction mixture was poured into a saturated aqueous NH_4Cl solution 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 silica gel column chromatography (from 20% to 50% ethyl acetate in hexane) afforded the coupling product **15** (3.04 g, 84%) as a pale yellow oil: $[\alpha]_D^{22}$ 5.28 (*c* 0.63, $CHCl_3$); IR (NaCl, cm^{-1}) 3439, 2963, 2930, 2872, 2211, 1719, 1618; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, 1H, $J = 15.1, 12.0$ Hz), 6.47 (ddd, 1H, $J = 12.0, 1.5, 0.98$ Hz), 5.91 (d, 1H, $J = 15.1$ Hz), 3.84 (m, 1H), 3.76 (s, 3H), 2.37 (ddd, 1H, $J = 14.4, 5.1, 1.7$ Hz), 2.03 (d, 3H, $J = 0.98$ Hz), 1.66 (dd, 1H, $J = 14.4, 8.8$ Hz), 1.62 (ddd, 1H, $J = 13.0, 3.4, 1.7$ Hz), 1.51 (s, 3H), 1.27 (s, 3H), 1.24 (dd, 1H, $J = 13.0, 10.5$ Hz), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 138.9, 133.2, 127.1, 121.7, 89.8, 88.5, 67.3, 63.6, 51.6, 45.7, 39.8, 34.4, 29.8, 25.6, 21.6, 18.1; EI^+ HRMS found *m/z* 304.1679, calcd for $C_{18}H_{24}O_4$ M^+ 304.1675.

(2*E*,4*E*)-7-[(1′*R*,2′*R*,4′*S*)-4′-Acetoxy-2′-hydroxy-2′,6′,6′-trimethylcyclohexylidene]-5-methylhepta-2,4,6-trien-1-ol (2). To a solution of 3-acetoxy allenic aldehyde[28] (1.96 g, 6.21 mmol) in methanol (60 mL) was added sodium borohydride (707 mg, 18.7 mmol) at 0 °C. The reaction mixture was stirred for 15 min at room temperature, and water was added dropwise, 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 to afford alcohol **2** (1.95 g, 98%) as a pale yellow solid: $[\alpha]_D^{21}$ −6.91 (*c* 0.45, $CHCl_3$); IR (KBr, cm^{-1}) 3397, 2969, 2926, 2861, 1935, 1734, 1657, 1640, 1456, 1368; ^1H NMR (400 MHz, $CDCl_3$) δ 6.55 (ddt, 1H, $J = 15.1, 11.2, 1.5$ Hz), 6.02 (d, 1H, $J = 11.2$ Hz), 6.00 (s, 1H), 5.85 (dt, 1H, $J = 15.1, 6.0$ Hz), 5.37 (tt, 1H, $J = 11.5, 4.2$ Hz), 4.24 (br m, 2H), 2.28 (ddd, 1H, $J = 12.9, 4.1, 2.2$ Hz), 2.04 (s, 3H), 1.99 (ddd, 1H, $J = 12.44, 4.2, 2.2$ Hz), 1.76 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.30−1.50 (m, 2H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 170.4, 132.4, 131.8, 127.8, 126.6, 117.4, 102.8, 72.6, 68.0, 63.6, 45.4, 45.2, 35.6, 32.0, 31.2, 29.2, 21.4, 13.8; EI^+ HRMS found *m/z* 320.1997, calcd for $C_{19}H_{28}O_4$ M^+ 320.1987.

(5*RS*)-Hydroxy-3-[(1′*E*)-2′-(1″*S*,2″*R*,4″*S*)-4″-*tert*-butyldimethylsiloxy-1″,2″-epoxy-2″,6″,6″-trimethylcyclohex-1″-ylethen-1′-yl]-2-(5*H*)furanone (19). To a suspension of silylfuran−Wittig reagent **17**[34] (2.16 g, 4.02 mmol) in diethyl ether (20 mL) was added dropwise ^nBuLi (1.6 M in hexane, 2.52 mL, 4.02 mmol) at 0 °C. After the mixture was stirred for 10 min at 0 °C, a solution of **4** (1.0 g, 3.35 mmol) in diethyl ether (5 mL) was added, and the reaction mixture was stirred for 3 h at room temperature. It was filtered through a pad of Celite. Water was added to the filtrate, and the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude silylfuran **18**, which was used in the next reaction without further purification.

A solution of the crude **18** and tetraphenylporphine (5 mg) in dichloromethane (50 mL) was irradiated with a halogen−tungsten lamp under oxygen atmosphere for 30 min at −78 °C. After the mixture was allowed to warm to room temperature, the solvents were removed in vacuo. Purification by silica gel column chromatography (from 2% to 50% ethyl acetate in hexane) afforded γ-hydroxybutenolide **19** (2.01 g, 77% for two steps) as a yellow oil: $[\alpha]_D^{21}$ −47.49 (*c* 0.34, $CHCl_3$); IR (NaCl, cm^{-1}) 3376, 2957 2932, 2859, 1769, 1659; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 1H, $J = 15.6$ Hz), 6.93 (s, 1H), 6.27 (d, 1H, $J = 15$ Hz), 5.95 (s, 1H), 4.97 (br s, 1H), 3.83 (m, 1H), 2.23 (ddd, 1H, $J = 14.6, 5.1, 1.5$ Hz), 1.65 (dd, 1H, $J = 14.6, 8.3$ Hz), 1.49 (ddd, 1H, $J = 12.9, 3.4, 1.7$ Hz), 1.26 (dd, 1H, $J = 12.9, 10.0$ Hz), 1.16 (s, 3H), 0.92 (s, 3H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 143.0, 135.6, 131.3, 120.7, 96.2, 70.6, 67.5, 64.6, 46.8, 41.1, 35.0, 29.3, 25.8, 24.9, 19.9, 18.1, −4.78, −4.81; EI^+ HRMS found *m/z* 394.2175, calcd for $C_{24}H_{38}O_5Si$ M^+ 394.2173.

(3*Z*,5*E*)-4-Allyloxycarbonyl-6-[(1′*S*,2′*R*,4′*S*)-4′-*tert*-butyldimethylsiloxy-1′,2′ -epoxy-2′,6′,6′-trimethylcyclohex-1′-yl]-1,1-dibromohexa-1,3,5-triene (28). A solution of the crude **18** and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (5 mg) in dichloromethane (30 mL) was irradiated with a halogen−tungsten lamp under oxygen atmosphere for 30 min at −78 °C (γ-hydroxybutenolide **19** was formed in situ). After the reaction mixture was allowed to warm to room temperature, diisopropylethylamine (1.75 mL, 10.05 mmol) was added. After the resulting mixture was stirred for 3 h at room temperature, allyl bromide (0.43 mL, 5.03 mmol) was added dropwise, and then the mixture was stirred for 1 h [(*Z*)-β-alkoxycarbonyldienal **27** was formed in situ]. To a solution of carbon tetrachloride (4.44 g, 13.40 mmol) and triphenylphosphine (7.00 g, 26.80 mmol) in dichloromethane (20 mL) was added dropwise the reaction mixture at −60 °C. After the mixture was stirred for 1 h at the same temperature, hexane was added, the precipitate was removed by filtration through a pad of Celite, and then the solvents were removed in vacuo. Purification by silica gel column chromatography (from 2% to 5% ethyl acetate in hexane) afforded dibromide **28** (1.05 g, 53% from **4**) as a yellow oil.

Data for **27**: $[\alpha]_D^{22}$ −77.47 (*c* 0.97, $CHCl_3$); IR (NaCl, cm^{-1}) 2959, 2930, 2857, 1734, 1680, 1626, 1589, 1472, 1381, 1345; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, 1H, $J = 7.6$ Hz), 6.50 (d, 1H, $J = 15.6$ Hz), 6.36 (d, 1H, $J = 15.6$ Hz), 6.10 (d, 1H, $J = 7.6$ Hz), 5.98 (ddt, 1H, $J = 17.1, 10.5, 6.1$ Hz), 5.42 (dd, 1H, $J = 17.1, 1.2$ Hz), 5.34 (dd, 1H, $J = 10.3, 1.2$ Hz), 4.83 (m, 2H), 3.84 (m, 1H), 2.24 (ddd, 1H, $J = 14.6, 4.9, 1.5$ Hz), 1.65 (dd, 1H, $J = 14.4, 8.1$ Hz), 1.50 (ddd, 1H, $J = 13.2, 3.4, 1.5$ Hz), 1.25 (dd, 1H, $J = 13.2, 9.8$ Hz), 1.17 (s, 3H), 1.13 (s, 3H), 0.95 (s, 3H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 165.5, 147.9, 138.5, 129.8, 128.9, 120.3, 70.2, 67.6, 66.6, 64.5, 46.6, 41.1, 35.1, 29.2, 25.8, 25.1, 20.0, 15.3, −4.75, −4.79; EI^+ HRMS found *m/z* 434.2487, calcd for $C_{24}H_{38}O_5Si$ M^+ 434.2488.

Data for **28**: $[\alpha]_D^{21}$ −45.81 (*c* 1.19, $CHCl_3$); IR (NaCl, cm^{-1}) 2957, 2930, 2858, 1721, 1462, 1383, 1364; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 1H, $J = 11.2$ Hz), 6.44 (d, 1H, $J = 11.2$ Hz), 6.30 (d, 1H, $J = 15.6$ Hz), 6.26 (d, 1H, $J = 15.6$ Hz), 5.98 (ddt, 1H, $J = 17.1, 10.2, 5.9$ Hz), 5.39 (dd, 1H, $J = 17.1, 1.2$ Hz), 5.30 (dd, 1H, $J = 10.5, 1.2$ Hz), 4.75 (m, 2H), 3.85 (m, 1H), 2.24 (ddd, 1H, $J = 14.4, 5.1, 1.5$ Hz), 1.64 (dd, 1H, $J = 14.4, 8.3$ Hz), 1.50 (ddd, 1H, $J = 13.2, 3.4, 1.5$ Hz), 1.24 (dd, 1H, $J = 13.2, 10.0$ Hz), 1.18 (s, 3H), 1.12 (s, 3H), 0.96 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 133.4, 131.5, 131.4, 130.0, 98.2, 70.3, 67.2, 65.8, 64.6, 47.0, 41.3, 35.1, 29.3, 25.9, 25.0, 20.0−4.7, −4.8; EI^+ HRMS found *m/z* 588.0916, calcd for $C_{25}H_{38}O_4{}^{79}Br_2Si$ M^+ 588.0907.

(3*Z*,5*E*)-4-Allyloxycarbonyl-6-[(1′*S*,2′*R*,4′*S*)-4′-hydroxy-1′,2′-epoxy-2′,6′,6′-trimethylcyclohex-1′-yl]hexa-3,5-dien-1-yne (29). To a solution of **28** (1.50 g, 2.54 mmol) in THF (25 mL) was added tetra-*n*-butylammonium fluoride (4.00 g, 15.2 mmol) at room temperature. After being stirred for 20 h at 45 °C, the reaction mixture was poured into a saturated aqueous NH_4Cl solution 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 10% to 30% ethyl acetate in hexane) afforded terminal acetylene **29** (652 mg, 81%) as an orange oil, which was immediately used in the next reaction: IR (NaCl, cm^{-1}) 3412, 3293, 3086, 2963, 2930, 2874, 2097, 1725, 1649, 1582, 1453, 1383, 1366, 1223, 1163, 1049; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 2H), 5.99 (ddt, 1H, J = 17.1, 10.5, 5.9 Hz), 5.84 (d, 1H, J = 2.7 Hz), 5.42 (dd, 1H, J = 17.1, 1.2 Hz), 5.29 (dd, 1H, J = 10.5, 1.2 Hz), 4.80 (m, 2H), 3.88 (m, 1H), 3.42 (d, 1H, J = 2.7 Hz), 2.37 (ddd, 1H, J = 14.2, 5.1, 1.7 Hz), 1.50−1.70 (m, 2H), 1.23 (dd, 1H, J = 13.2, 10.5 Hz), 1.19 (s, 3H), 1.12 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 142.9, 131.8, 131.5, 128.8, 119.0, 113.1, 87.1, 80.0, 69.9, 67.3, 65.8, 64.0, 46.9, 40.8, 35.2, 29.3, 24.8, 19.8; EI^+ HRMS found *m/z* 316.1684, calcd for $C_{19}H_{24}O_4$ M^+ 316.1673.

(5*Z*)-[(2′*E*)-4′-Hydroxy-2′-methyl-1′-butenylidene]-3-[(1″*E*)-2″-(1‴*S*,2‴*R*,4′″*S*)-4‴-hydroxy-1‴,2‴-epoxy-2‴,6‴,6‴-trimethylcyclohex-1‴-ylethen-1″-yl]-2-(5*H*)furanone (3). To a solution of **29** (650 mg, 2.04 mmol) and **13** (450 mg, 2.28 mmol) in triethylamine (20 mL) were added tetrakis(triphenylphosphine)palladium (236 mg, 0.20 mmol) and cuprous iodide (40 mg, 0.20 mmol) at room temperature. The reaction mixture was stirred at room temperature until **29** was completely consumed by monitoring with TLC (ca. 1 h), and formic acid (0.30 mL, 6.52 mmol) was added dropwise. After being stirred for the additional 20 h, the resulting mixture was poured into a saturated aqueous NH_4Cl solution 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 70% ethyl acetate in hexane) afforded ylidenebutenolide **3** (345 mg, 49%) as an orange solid: $[\alpha]_D^{21}$ −38.52 (*c* 0.83, $CHCl_3$); IR (KBr, cm^{-1}) 3420, 2965, 2928, 1755, 1640, 1440, 1381, 1248, 1154, 1121, 1047; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, 1H, J = 15.6 Hz), 7.04 (s, 1H), 6.37 (d, 1H, J = 15.6 Hz), 5.97 (t, 1H, J = 6.6 Hz), 5.65 (s, 1H), 4.36 (d, 2H, J = 6.6 Hz), 3.90 (m, 1H), 2.40 (ddd, 1H, J = 14.4, 5.1, 1.7 Hz), 1.50−1.70 (m, 2H), 1,25 (m, 1H), 1.21 (s, 6H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 146.6, 136.9, 134.3, 133.9, 125.9, 121.5, 117.6, 70.4, 67.5, 64.1, 59.5, 47.0, 40.9, 35.3, 29.4, 24.9, 19.8, 15.5; EI^+ HRMS found *m/z* 346.1788, calcd for $C_{20}H_{26}O_5$ M^+ 346.1779.

2-[(((2′*E*,4′*E*)-7′-(1″*R*,2″*R*,4″*S*)-4″-Acetoxy-2″-hydroxy-2″,6″,6″-trimethylcyclohexylidene)-5′-methylhepta-2′,4′,6′-trienyl)sulfonyl]benzothiazole (32). To a solution of **2** (465 mg, 1.45 mmol), 2-mercaptobenzothiazole (291 mg, 1.74 mmol), and triphenylphosphine (456 mg, 1.74 mmol) in THF (15 mL) was added dropwise diisopropyl azodicarboxylate (0.27 mL, 1.88 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature, and then 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 20% to 50% ethyl acetate in hexane) afforded thioether (529 mg, 78%) as a pale yellow solid: $[\alpha]_D^{21}$ −7.02 (*c* 0.89, $CDCl_3$); IR (KBr, cm^{-1}) 3426, 3061, 3029, 2965, 2926, 1933, 1719, 1632, 1458, 1427, 1372, 1250, 1182, 1163, 1109, 1073, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, 1H, J = 7.8, 1.2 Hz), 7.76 (dd, 1H, J = 7.8, 1.2 Hz), 7.42 (ddd, 1H, J = 7.8, 7.8, 1.2 Hz), 7.30 (ddd, 1H, J = 7.8, 7.8, 1.2 Hz), 6.65 (dd, 1H, J = 14.6, 11.0 Hz), 5.98 (d, 1H, J = 11.0 Hz), 5.96 (s, 1H), 5.86 (dt, 1H, J = 14.6, 7.6 Hz), 5.37 (tt, 1H, J = 11.5, 4.2 Hz), 4.10 (d, 2H, J = 7.8 Hz), 2.27 (ddd, 1H, J = 12.7, 3.9, 2.2 Hz), 2.03 (s, 3H), 1.98 (ddd, 1H, J = 12.4, 4.4, 2.2 Hz), 1.74 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.30−1.50 (m, 2H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 170.4, 166.2, 153.2, 135.3, 132.8, 131.0, 126.4, 126.3, 126.0, 124.2, 121.5, 121.0, 117.5, 102.7, 72.5, 68.0, 45.4, 45.2, 36.2, 35.6, 32.0, 31.2, 29.1, 21.4, 13.8; EI^+ HRMS found *m/z* 469.1748, calcd for $C_{26}H_{31}O_3NS_2$ M^+ 469.1743.

To a solution of the thioether (500 mg, 1.07 mmol) in ethanol (10 mL) was added dropwise a solution of ammonium heptamolybdate tetrahydrate (132 mg, 0.11 mmol) in hydrogen peroxide (30 wt % in water, 2.0 mL) at 0 °C. After being stirred for 1 h at the same temperature, the reaction mixture was poured into brine and then extracted with diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by short alumina column chromatography (from 30% to 50% ethyl acetate in hexane) afforded sulfone **32** (474 mg, 89%) as a pale yellow solid: $[\alpha]_D^{21}$ −6.15 (*c* 0.77, $CDCl_3$); IR (KBr, cm^{-1}) 3356, 2976, 2928, 1935, 1725, 1630, 1472, 1426, 1375, 1331, 1248, 1148, 1109, 1073; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, 1H, J = 7.8, 1.2 Hz), 8.01 (dd, 1H, J = 7.8, 1.2 Hz), 7.65 (ddd, 1H, J = 7.8, 7.8, 1.2 Hz), 7.59 (ddd, 1H, J = 7.8, 7.8, 1.2 Hz), 6.53 (dd, 1H, J = 15.1, 11.7 Hz), 5.95 (d, 1H, J = 11.7 Hz), 5.93 (s, 1H), 5.61 (dt, 1H, J = 15.1, 7.8 Hz), 5.36 (tt, 1H, J = 11.7, 4.4 Hz), 4.32 (d, 2H, J = 7.8 Hz), 2.27 (ddd, 1H, J = 12.7, 4.4, 2.0 Hz), 2.03 (s, 3H), 1.97 (ddd, 1H, J = 12.7, 4.4, 2.0 Hz), 1.57 (s, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 1.30−1.50 (m, 2H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 170.4, 165.6, 152.6, 137.0, 136.8, 135.3, 127.9, 127.6, 125.5, 125.4, 122.3, 117.6, 115.1, 102.4, 72.4, 67.9, 59.0, 45.3, 45.2, 35.6, 31.9, 31.0, 29.0, 21.3, 13.6; EI^+ HRMS found *m/z* 501.1637, calcd for $C_{26}H_{31}O_5NS_2$ M^+ 501.1642.

(5*Z*)-[(2′*E*)-2′-Methyl-4′-oxo-2′-butenylidene]-3-[(1″*E*)-2″-(1‴*S*,2‴*R*,4‴*S*)-4 ‴-hydroxy-1‴,2‴-epoxy-2‴,6‴,6‴-trimethylcyclohex-1‴-ylethen-1″-yl]-2-(5*H*)furanone (33). To a solution of **3** (180 mg, 0.51 mmol) in diethyl ether (6.0 mL) was added manganese dioxide (3.0 g) at room temperature. After being stirred at the same temperature for 5 min, the reaction mixture was filtered through a pad of Celite. The solvents were removed in vacuo to afford the crude aldehyde **33**, which was used to the next reaction without further purification.

Peridinin (1). To a solution of **32** (261 mg, 0.51 mmol) and the crude **33** in THF (10 mL) was added dropwise sodium bis(trimethylsilyl)amide (1.0 M in THF, 1.00 mL, 1.00 mmol) at −78 °C in the dark. After being stirred for 5 min at the same temperature, the reaction mixture was poured into brine 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 50% ethyl acetate in hexane) in the dark afforded a mixture of *all-trans*-peridinin (**1**) and its 15-*cis* isomer (**34**) (168 mg, 50%, ca. 1:3 based on ^{1}H NMR analysis) as a red film.

A solution of a mixture of *all-trans*-peridinin and its 15-*cis* isomer in benzene (2.0 mL) was left at room temperature in the dark. After 3 days, a thermodynamic equilibrium was reached, *E*:*Z* = >5:1, and then purification and partial separation by preparative HPLC [column, Develosil CN-UG (0.6 × 25 cm); mobile phase, acetone/*n*-hexane = 1/10; flow rate, 1.54 mL/min; UV detection, 450 nm; retention time, (*all-trans* isomer) 50 min., (15-*cis* isomer) 53 min] in the dark afforded the desired optically active peridinin (**1**) as a red powder: IR (KBr, cm^{-1}) 3418, 2963, 2926, 2857, 1929, 1738, 1657, 1524, 1456, 1439, 1365, 1250, 1161, 1121, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, 1H, J = 15.6 Hz), 7.02 (s, 1H), 6.61 (dd, 2H, J = 14.2, 11.7 Hz), 6.51 (dd, 1H, J = 14.2, 10.5 Hz), 6.45 (d, 1H, J = 11.5 Hz), 6.384 (dd, 1H, J = 14.4, 10.5 Hz), 6.377 (d, 1H, J = 15.6 Hz), 6.11 (d, 1H, J = 11.2 Hz), 6.06 (s, 1H), 5.73 (s, 1H), 5.38 (tt, 1H, J = 11.7, 4.4 Hz), 3.90 (m, 1H), 2.40 (ddd, 1H, J = 14.2, 5.0, 1.5 Hz), 2.28 (ddd, 1H, J = 13.0, 4.2, 2.0 Hz), 2.23 (s, 3H), 2.04 (s, 3H), 1.99 (ddd, 1H,

J = 12.4, 4.0, 2.0 Hz), 1.80 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.07 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 170.4, 168.8, 146.8, 138.0, 137.2, 136.3, 134.0, 133.9, 133.6, 133.0, 131.5, 128.9, 128.1, 124.8, 121.8, 119.2, 117.6, 103.3, 72.7, 70.4, 67.9, 67.5, 64.2, 47.1, 45.4, 45.2, 40.9, 35.8, 35.3, 32.1, 31.3, 29.5, 29.2, 24.9, 21.4, 19.9, 15.4, 14.0; EI$^+$ HRMS found m/z 630.3544, calcd for $C_{39}H_{50}O_7$ M$^+$ 630.3554. For CD spectra, see Supporting Information.

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Supporting Information Available: Experimental procedure and characterization data for compounds **4**−**14**, **16**−**26**, and model studies (**29a** and **30**) and copies of ^{1}H and ^{13}C NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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