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Total Synthesis of Peridinin and Related C_{37}-Norcarotenoid Butenolides

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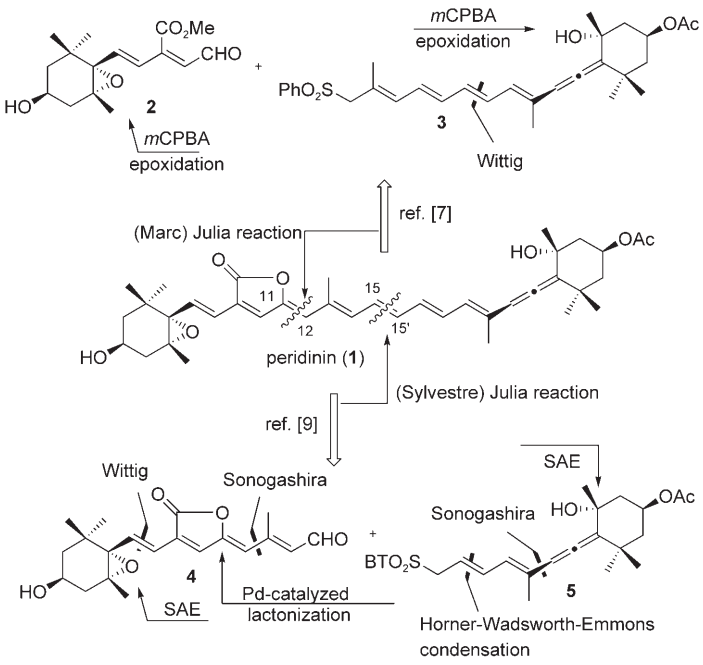
Abstract: As an extension of our synthesis of symmetrical carotenoids, the preparation of the highly functionalized C_{37}-norcarotenoid butenolide peridinin (**1**), its 6′-*epi*- and 11′*Z* stereoisomers has been completed. Featuring a central dihalogenated C_8 linchpin unit **6**, two synthetic routes, differing in the ordering of the last three steps were explored by using the C3,C3′-bisdehydroxylated target as the model system. The first route uses the combination of a modified *Z*-selective Julia reaction and two sequential Stille couplings, the last one producing the isomerisation of the polyene *Z* double bond. The second route inverts these steps and makes the isolation of the 11′*Z* stereoisomers as major products possible. An efficient *Z* to *E* isomerisation of the final carotenoid skeleton simply uses the Stille reaction conditions at ambient temperature. As the reaction of bromoallene **12** with alkenylstannane **11** occurs with inversion of configuration, 6′-*epi*-peridinin could also be prepared by route A. The advantages and limitations of the sequential Stille cross-coupling approach to carotenoids are highlighted.

Keywords: carotenoids · Julia reaction · peridinin · Stille reaction · total synthesis

Introduction

Carotenoids are ubiquitous natural pigments widely distributed across all kingdoms[1] and their isolation from a variety of species from bacteria, yeast, algae, plants, animals and even humans has been documented.[1] These highly conjugated polyenes play fundamental roles as photoprotective and antioxidation agents, and their activities have been linked to chemoprevention of various diseases, including cancer, atherosclerosis and macular degeneration in humans. They are also dietary sources of vitamin A and other naturally occurring retinoids.[2] In addition, carotenoids are components of photosynthetic light-harvesting devices of both plants and microalgae.

The most abundant photosynthetic pigment is peridinin (**1**) (Scheme 1), a member of the xantophylls, a subgroup of hydroxylated carotenoids. Among other sources, peridinin (**1**) has been isolated from planktonic dinoflagelates, such as *Amphidinium carterae*, which are causally linked to "red tide" episodes.[3] A fascinating supramolecular structure composed of two chlorophyll A molecules and four peridinin units embebbed in a protein (PCP complex) and held in place by noncovalent interactions in *A. carterae* has been re-



Scheme 1. Previous approaches to peridinin (**1**), highlighting the key disconnections.

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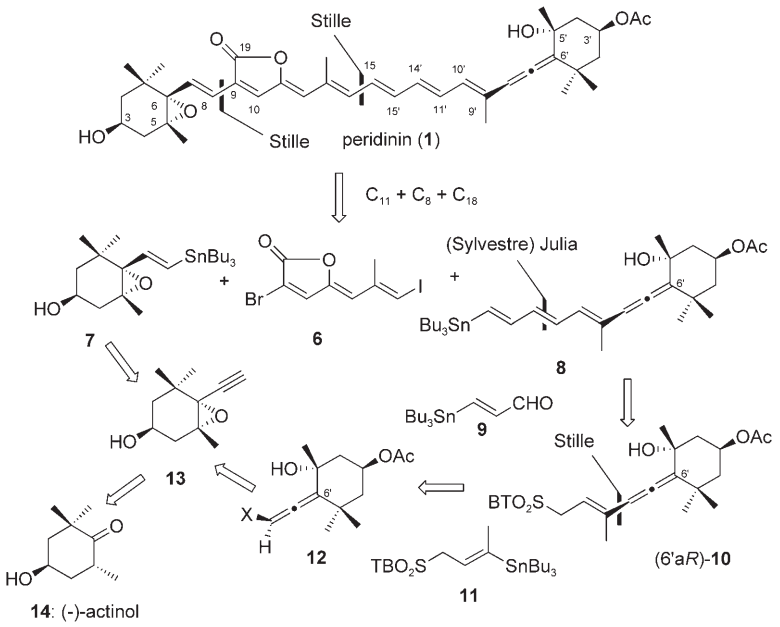
vealed by X-ray crystallography.[4] The structural details provided by this architecture might help us to understand the efficiency of the photosynthetic assemblies responsible for light harvesting in *A. carterae* and, moreover, serve as an inspiration for the design of novel alternative energy-production systems.

Although isolated in 1890, the three-dimensional structure of peridinin (**1**) was determined by Liaaen-Janssen and Rapoport in 1976,[5] and was further supported by NMR studies[6] and later confirmed by total synthesis.[7] Peridinin exhibits a highly functionalized C_{37}-norcarotenoid structure with a γ-alkylidenebutenolide as part of the polyene chain, a quite uncommon feature, which is present in only a few of the approximately 700 naturally occurring carotenoids.[1] Its oxygenation pattern adds stereochemical complexity. As a target of total synthesis, stereocontrol will be required not only during the build up of the polyene skeleton, but also in the generation of the remaining stereochemical elements: the three hydroxylated carbons atoms (one of them functionalized as an acetate), the oxirane, the allene chiral axis and the *Z*-γ-alkylidenebutenolide unit. Not surprisingly, the first total synthesis of enantiopure peridinin was described by Ito et al. in 1990.[7] The synthetic strategy of Ito's approach rested on a (Marc) Julia reaction of C_{15} (**2**) and C_{22} (**3**) fragments[8] as the last and crucial step to construct the complete C_{37}-norcarotenoid skeleton and concomitantly the γ-alkylidenebutenolide ring (Scheme 1). The sequence suffered from poor stereocontrol in some of the double bond formation steps as well as low substrate-induced diastereoselectivity in the steps setting up the correct configuration at the oxygenated positions of the terminal cyclohexane rings. The low yield and lack of stereocontrol of the Julia reaction, and the tedious separations of double-bond isomers considerably reduced the efficacy of the synthesis (≪1% overall yield).

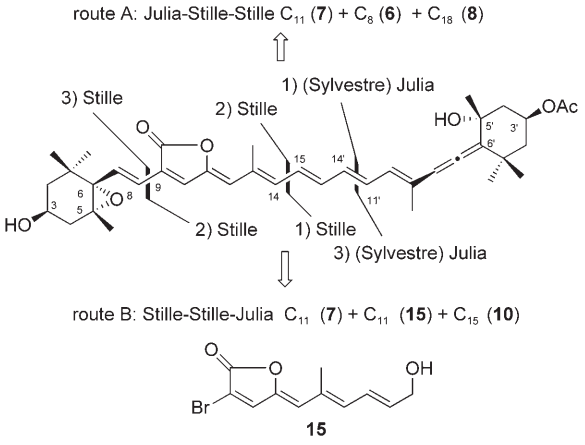
A decade later, Katsumura and co-workers described a fully stereocontrolled synthesis of peridinin (8% overall yield) based on a final modified (Sylvestre) Julia olefination of **4** and **5** as the key connective step to construct the complete C_{37} skeleton.[9] The generation of the five stereocenters, as well as the formation of the chiral axis and all the polyene double bonds of peridinin (**1**) proceeded with the appropriate stereocontrol. The Julia olefination between allyl benzothiazolyl (BT) sulfone **5** and the corresponding aldehyde **4** afforded a mixture of all-*trans* and (15*Z*)-peridinin in a 1:3 ratio (Scheme 1), which was further enriched in natural peridinin (**1**) after stirring for three days in benzene at ambient temperature (reaching a 5:1 thermodynamic equilibrium of all-*trans* and (15*Z*)-peridinin).

Departing from the classical double-bond-forming reactions used in the above synthetic sequences, there has been recent interest[10,11] in the development of new strategies towards the synthesis of these polyenes. Alternative approaches to symmetrical carotenoids[10a] and highly functionalized carotenoid butenolides[10b] feature the generation of single bonds connecting Csp^2 atoms through Pd-catalyzed cross-coupling reactions.[12] We conceived the synthesis of peridinin (**1**) by convergent and sequential Stille cross-coupling reactions[13] of a central C_8-γ-alkylidenebutenolide linchpin **6**[8] containing halogens of modulated reactivity, and functionalized C_{11} (**7**) and C_{18} (**8**) alkenylstannanes comprising all remaining carbons of the skeleton (Scheme 2).

In addition, the retrosynthesis contemplated another Stille cross-coupling of stannylated BT-sulfone **11** and haloallene **12**, to afford the functionality required for a (Sylvestre) Julia olefination[14] of **9** and **10**. An attractive feature of the retrosynthetic scheme rests on the fact that both fragments **7** and **12** converge in alkynyloxirane **13**, which was envisaged to derive from (−)-actinol **14**, a common building block for the industrial synthesis of xanthophylls.[15] Appropriate functionalisations of **13** include a regio- and stereoselective palladium-catalyzed hydrostannation[16] to **7** and the S_N2'-like ring opening of alkynyloxiranes[17] to haloallenes **12**, both of which are precedented. The Sharpless asymmetric epoxidation (SAE)[18] of a precursor allyl alcohol would set up the absolute configuration of alkynyloxirane **13**. The sequence was in effect validated, although on implementation of this scheme, we first found an inconsequential *Z* outcome for the geometry of the olefin obtained in the (Sylvestre) Julia olefination of **9** and **10** and, most importantly, either a nonstereoselective outcome or a complete inversion



Scheme 2. Retrosynthetic analysis of peridinin (**1**) based on sequential Stille cross-coupling reactions.



Scheme 3. Two routes to peridinin (**1**) explored in this work, with the order and nature of the last three synthetic steps.

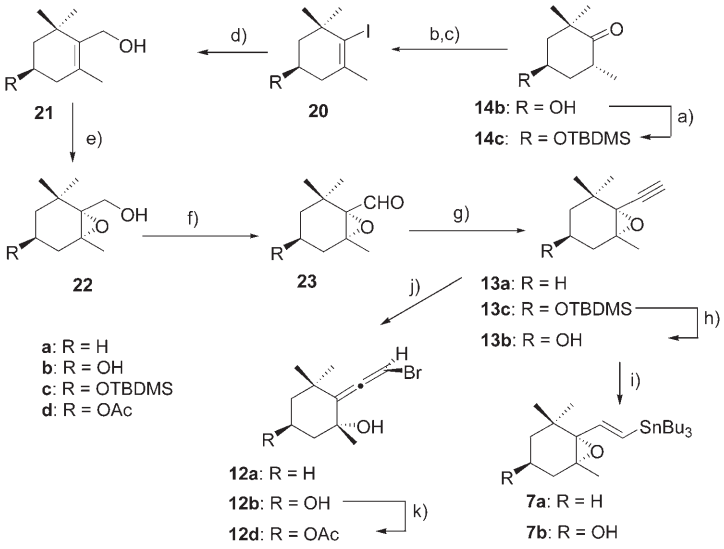
of configuration of the chiral axis in the Stille cross-coupling of **11** and **12**. Our efforts thus culminated in the preparation of the diastereomer of peridinin (**1**) at the allene axis (6′-*epi*-peridinin (6′-*epi*-**1**)).[10b]

We present herein a full report of our work in this field, including the evaluation of two closely related alternative synthetic approaches to these naturally occurring C_{37}-norcarotenoids by using model systems, and the stereocontrolled synthesis of peridinin (**1**).

Results and Discussion

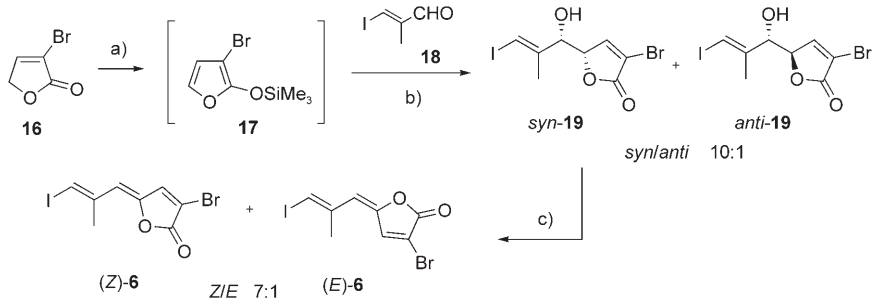
The retrosynthetic scheme depicted in Scheme 2 is one of the approaches to these natural products explored in this work. It will be referred to as route A, a sequence that connects fragments **8**, **6** and **7**, and therefore follows a $C_{18}+C_8+C_{11}$ construction tactic. The last two steps of the sequence to form the C8–C9 and C14–C15 bonds are both Stille reactions and are preceded by the Julia condensation that forms the C11′–C14′ olefin. A closely related route, route B, featuring a $C_{11}+C_{11}+C_{15}$ scheme, differs from A in the order of the last three key steps, and disconnects the C_{37}-norcarotenoid skeleton at the C8–C9 (Stille) and the C11′–C14′ (Julia) bonds after the allylBT-sulfone functionality has been incorporated through another Stille coupling. Required fragments are the common **7** and **10**, and bromobutenolide **15** (Scheme 3).

With the aim to determine the merits and disadvantages of each strategy, we decided to construct a model of peridinin that preserves all carbons of the C_{37}-norcarotenoid skeleton but lacks the hydroxyl groups at positions C3 and C3′. The fragments required for the assembly of the model system and the parent natural product were prepared by the routes described in Schemes 4, 5 and 6.

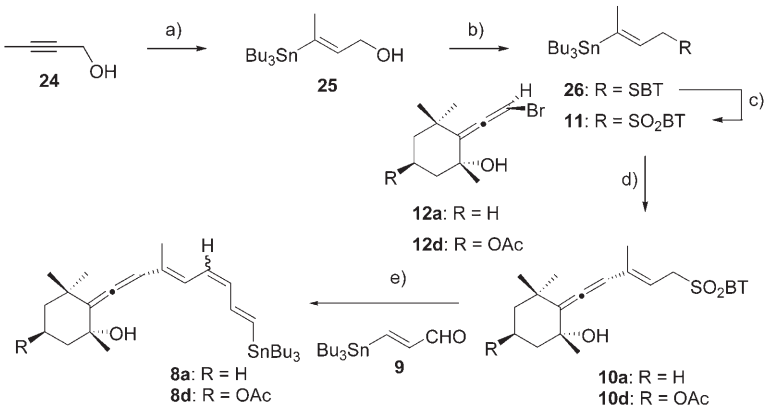


Scheme 5. a) TBDMSCl, imidazole, DMF, 25 °C (83 %); b) $H_2NNH_2{\cdot}H_2O$, Et_3N, EtOH, reflux; c) I_2, DBN, EtO_2 (2 steps, 80 %); d) *t*BuLi, $(CH_2O)_n$, THF, −78 °C, 15 h (71 %); e) D-(−)-DET, $Ti(OiPr)_4$, TBHP, CH_2Cl_2, −20 °C (98 % for **22a**, 98 % for **22c**); f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 −60 to 25 °C (89 % for **23a**, 91 % for **23c**); g) LDA, $TMSCHN_2$, THF, −78 to 25 °C (84 % for **13a**, 92 % for **13c**); h) TBAF, THF, 25 °C, 2 h (85 % for **13b**); i) $[PdCl_2(PPh_3)_2]$, Bu_3SnH, THF, 25 °C (70 % for **7a**, 68 % for **7b**); j) CuBr, NH_4Br, HBr, Et_2O, −10 °C (86 % for **12a**, 85 % for **12b**); k) Ac_2O, py, 25 °C, 16 h (85 %). TBDMS = *tert*-butyldimethylsilyl; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene; DET = diethyl D-tartrate; TBHP = *tert*-butyl hydroperoxide; LDA = lithium diisopropylamide; TBAF = tetrabutylammoinium fluoride.

Scheme 4 depicts the preparation of the C_8 γ-alkylidenebutenolide **6** linchpin, which contains two different halogens. Among the other options available,[19] we selected the vinylogous (extended) Mukaiyama aldol reaction[20] of 3-bromo-2-trimethylsiloxyfuran **17**[21] and 3-iodo-methacrolein **18**[22] for the construction of the butenolide ring, as developed by Brückner and co-workers.[21] Upon condensation at −90 °C under catalysis by BF_3, the corresponding hydroxyalkylbutenolide **19** was obtained with high *syn* diastereoselectivity (10:1 *syn*/*anti* ratio) in 86 % yield, as shown by the crystal structure of the major component (Figure 1). We have proposed an explanation for the simple diastereoselectivity in these vinylogous Mukaiyama



Scheme 4. a) Et_3N, TMSCl, CH_2Cl_2, 25 °C, 1 h; b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 1.5 h (86 % combined yield); c) DIAD, PPh_3, THF, −25 °C (65 %). DIAD = diisopropyl azodicarboxylate.



Scheme 6. a) $(Bu_3Sn)_2$, *n*-BuLi, CuCN, MeOH, THF, −10 °C (89 %); b) BTSH, PPh_3, DIAD, THF, 25 °C (98 %); c) 35 % H_2O_2, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, EtOH, 25 °C (56 %); d) (a*R*)-**12**, $[Pd(PhCN)_2Cl_2]$, $(iPr)_2NEt$, DMF/THF, 40 °C (69 % for **10a**, 64 % for **10d**); e) **10**, NaHMDS, THF, −78 °C, then **9** (79 % for **8a**, 70 % for **8d**). BTSH = 2-mercaptobenzothiazole; HMDS = hexamethyldisilazane.

aldol reactions based on high-level DFT computations of the 24 plausible diastereomeric transition structures.[23] It was our finding that the *syn* diastereomer most likely originates from a *g*+-like facial matching of the s-*trans* BF_3-activated acrolein and the *anti*-OTMS conformation of trimethylsiloxyfuran, which we selected as computational models. The major product *syn*(*lk*)-**19** (78 %) was converted through β elimination with excess PPh_3/DEAD[24] (THF, in the dark) into the desired halogen-differentiated alkylidenebutenolide **6**, a separable 7:1 mixture of *Z*/*E* isomers (65 %).

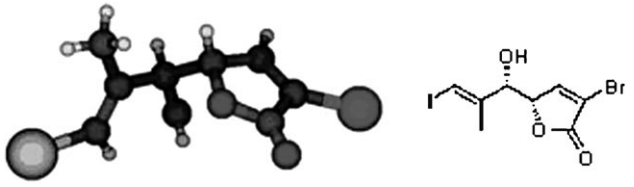


Figure 1. Stereostructure of the major *syn*-γ-hydroxyalkylbutenolide **19** (CCDC-267167) obtained in the BF_3-promoted vinylogous Mukaiyama aldol reaction of **17** and **18**.

Synthesis of the chiral cyclic end groups is shown in Scheme 5. Starting materials are β-cyclogeraniol **21a** and allyl alcohol **21c**. The latter was obtained uneventfully from the alkenyl iodide **20**, which was used as an intermediate in our synthesis of (3*R*,3′*R*)-zeaxanthin.[10] The conversion of **20** to the alkenyllithium derivative by iodine–lithium exchange (*t*BuLi, THF, −78 °C) was followed by trapping of the organometallic species with paraformaldehyde to furnish allyl alcohol **21c** in 71 % yield.

Although the SAE of β-cyclogeraniol **21a**[25] has been described,[26] we faced problems of reproducibility, extended reaction times (36 h), moderate yields (up to 80 %) and low enantioselectivities (no greater than 40 % *ee*). In contrast, stoichiometric quantities of $Ti(OiPr)_4$, 1.20 mol (−)-D-DET and 1.66 mol TBHP (CH_2Cl_2, −20 °C, 12 h) helped reduce these limitations and dramatically improved the performance of the process (89 % yield and >98 % *ee*, as determined by chiral HPLC on bromoallenes **12**). The facial selectivity of the SAE was also very high with **21c** under the same conditions. Epoxyalcohols **22** were oxidized to the corresponding aldehydes **23** by using Swern conditions[27] (89 and 91 % yield for **23a** and **23c**, respectively). Chain extension by Colvin rearrangement[28] to alkynyl oxiranes **13** proceeded efficiently (84 % yield for **13a** and 92 % for **13c**) upon treating aldehydes **23** with the anion of trimethylsilyldiazomethane. Enantiopure alkenylstannanes **7a** and **7b** were acquired in 70 and 68 % yield, respectively, by application of the palladium-catalyzed hydrostannation[16] ($[PdCl_2(PPh_3)_2]$, Bu_3SnH, THF, 25 °C, 10 min, 70 %), and then purified by reverse-phase chromatography. For the natural product, this proved to be more effective on the TBDMS-deprotected alkyne **13b** (TBAF, THF, 85 %). On the other hand, the conditions of Chemla[17a] (86 % HBr, CuBr, NH_4Br, Et_2O, −10 °C, 2.5 h) induced the opening of alkynyl oxiranes **13a** and **13b** with complete regio- and stereoselectively, and provided haloallenes **12**, products of S_N2' displacement, exclusively (86 % for **12a** and 85 % yield for **12b**). When the reaction was attempted on **13c**, the yield of the corresponding bromoallenol (a*R*)-**12c** was 29 %, and a small amount of its epimer (a*S*)-**12c** was also obtained. Furthermore, deprotection of (a*R*)-**12c** afforded alkynyl oxirane **13a**, the result of the secondary alcohol deprotection and the S_N2' reverse attack of the axial tertiary alcohol onto the allene bond.

Efficient acetylation of haloallene **12b** required treatment with acetic anhydride and pyridine at ambient temperature in order to minimize epimerisation of the chiral axis. Allene (a*R*)-**12d** was acquired in 85 % yield admixed with the a*S* diastereomer (>20:1). The minor diastereomer could be separated and the structure of the major (a*R*)-**12d** was secured by X-ray diffraction analysis (Figure 2).[29]

On the other hand, the alkenylstannane **25**[16a,30] prepared by stannylcupration of but-2-yn-1-ol **24**[31] was transformed into allyl benzothiazolyl sulfone **11** by a Mitsunobu variant (BTSH, PPh_3, DIAD, THF, 25 °C, 98 %)[32] and oxidation[33] of the sulfide **26** with hydrogen peroxide and the peroxymolybdate(VI) reagent[34] (35 % H_2O_2, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, EtOH, 25 °C, 56 %).

In the absence of precedents on the Stille cross-coupling reaction of chiral enantiopure haloallenes with alkenylstannanes, we decided to study the stereochemical outcome of the reaction between (a*R*)-**12d** and **11**. Only the related palladium-catalyzed cross-coupling reactions of enantiopure halogenated allenes with organozinc reagents had been reported by Vermeer,[35] and the stereoselectivity of the reac-

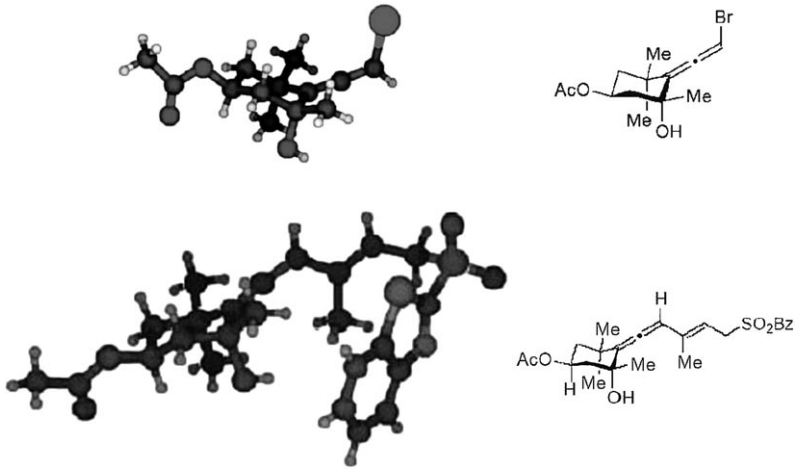
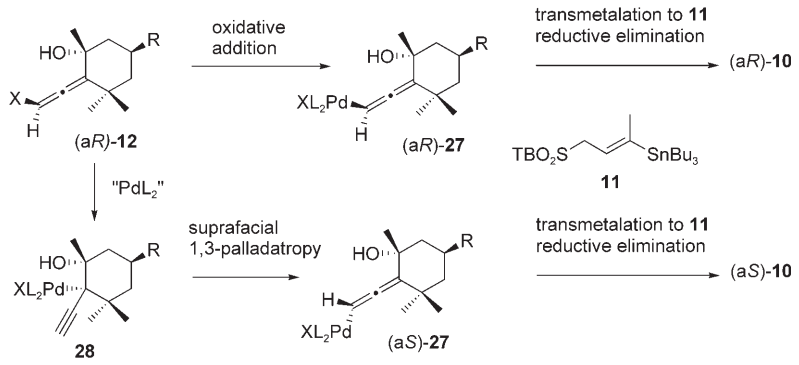


Figure 2. Stereostructure of (a*R*)-**12d** (CCDC-267168) and (*aS*)-**10d** (CCDC-267166).

tion was found to display halogen dependence (Br: inversion; I: retention). We were surprised to find low stereoselectivities in many of the trials, as inseparable mixtures of allenyl allyl sulfones **10**, differing not on the double-bond geometry, but on the configuration of the allene axis, were obtained. After extensive experimentation, varying the palladium catalysts ($[Pd_2(dba)_3]$/$[AsPh_3]$, $[Pd(PhCN)_2Cl_2]$, $[Pd_2(dba)_3]$/P*t*Bu$_3$, $[Pd_2(dba)_3]$/2-(di-*tert*-butylphosphino)biphenyl, solvent (DMF/THF, NMP, dioxane; NMP = *N*-methyl-2-pyrrolidinone), temperature (25 to 80 °C) and additives (amines), we found optimal conditions to acquire a single diastereomer from the coupling of bromoallene (a*R*)-**12** and **11**. These involve stirring a thoroughly degassed solution of both components and $[Pd(PhCN)_2Cl_2]$ in THF/DMF in the presence of Hünig's base at 40 °C (Scheme 6). The structure of the product, isolated in 69 (**10a**) and 64 % (**10d**) yield, was confirmed to be that of sulfone (a*S*)-**10** by X-ray diffraction (Figure 2), the product of formal inversion of configuration at the allene centre. No reversion of the stereochemical outcome was observed by using the coupling of **11** and the corresponding iodoallene (prepared in identical fashion from **13** using Chemla's method, 57 % HI, CuI, NH_4I, Et_2O, −10 °C, 2.5 h) instead.

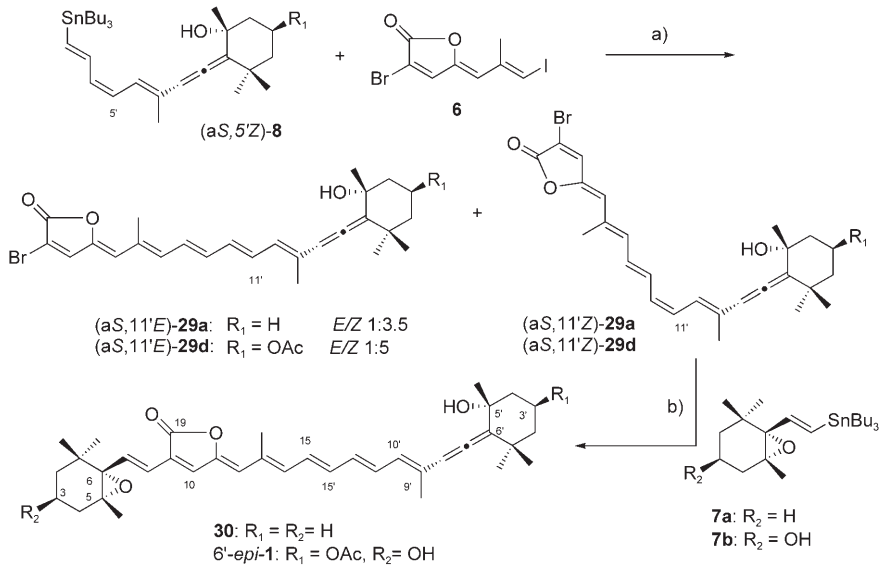
The allene axis inversion was interpreted as resulting from an *anti*-selective S_N2'-displacement of bromide by palladium to give **28**, followed by [1,3]-sigmatropic shift of propargyl- to allenyl-palladium, leading to (a*S*)-**27** before transmetalation and progression through the catalytic cycle (Scheme 7).[36]

Condensation of the anion formed by treatment of allenyl allyl BT-sulfone **10a** with NaHMDS and 3-(tributylstannyl)acrolein **9**[37] (THF, −78 to 25 °C) afforded a mixture of allenyl trienylstannanes **8a** in a 6:1 ratio of *E*/*Z* isomers and 79 % yield. On the other hand, **8d** was acquired in lower yield (70 %) and stereoselectivity (3:1 (*Z*)-**8d**/(*E*)-**8d**) by using the same protocol. Separation enabled characterization by ^{1}H NMR spectroscopy of the major isomer, (*Z*)-**8**, in each case, through analysis of proton coupling constants and NOE difference experiments. The minor isomer, presumably all-(*E*)-**8**, could not be characterized due to extensive degradation.



Scheme 7. Alternative pathways for the reaction of haloallenes **12** and stannane **11** catalyzed by palladium complexes.

The complete C_{37}-norcarotenoid skeleton was then assembled by combination of the described components. Following route A, we first adopted the conditions successfully employed for the coupling of **11** and **12** (Scheme 6). Although the coupling took place at ambient temperature in only 1 h, the *Z*/*E* isomer ratio (90 % yield) was disappointing (an approximately 50:50 mixture). We next turned our attention to the described coupling of 2-bromo-γ-alkylidenebutenolides and simple alkenylstannanes, which use Farina's conditions, namely, $[Pd_2(dba)_3]\cdot CHCl_3$ and $[AsPh_3]$ in NMP (Scheme 8).[39] Stannane (a*S*,5′*Z*)-**8** proved to be far less reactive than simple alkenylstannanes, and required stirring with butenolide **6** at ambient temperature for 18 h under the above described reaction conditions to reach completion. The extended reaction times proved, however, detrimental to the stereochemical integrity of the polyenes and a 50:50 mixture of isomers was obtained in 94 % yield. Fortunately, the beneficial effect of tetrabutylammonium phosphinate[40]



Scheme 8. a) $[Pd_2(dba)_3]\cdot CHCl_3$, $[AsPh_3]$, $Bu_4N^+Ph_2PO_2^-$, THF, 25 °C, 4.5 h (87% for **29a**) or 5.5 h (79% for **29d**); b) $[Pd_2(dba)_3]\cdot CHCl_3$, $[AsPh_3]$, $Bu_4N^+Ph_2PO_2^-$, THF, 55 °C, 20 h (21% for **30** yield based on recovered starting material) or 31 h (72% for 6′-*epi*-**1**).

$Bu_4N^+Ph_2PO_2^-$ enabled reduction of the reaction time to 4.5 h. The optimised 87% yield for **29a** (79% for **29d**) as a 3.5:1 ratio of the C11′–C12′ *Z*/*E* isomers (5:1 for **29d**) was obtained when BHT (BHT = 2,6-di-*tert*-butyl-4-methylphenol) was also added and the mixture was carefully deoxygenated. After separation by column chromatography, the major product was shown to be the *Z* isomer (a*S*,11′*Z*)-**29** through analysis of the ^{1}H NMR spectroscopic coupling constants and NOE-difference experiments, confirming that retention of configuration in the coupling partners had mostly taken place. The structure of the highly unstable minor isomer was assumed to be (a*S*,11′*E*)-**29**, in which the original *Z* double bond had been isomerised, a first indication of the sensitivity of the polyene geometry to the action of palladium catalysis (vide infra). Contrary to expectations, the minor isomer (a*S*,11′*E*)-**29** suffered extensive degradation and could not be characterized.

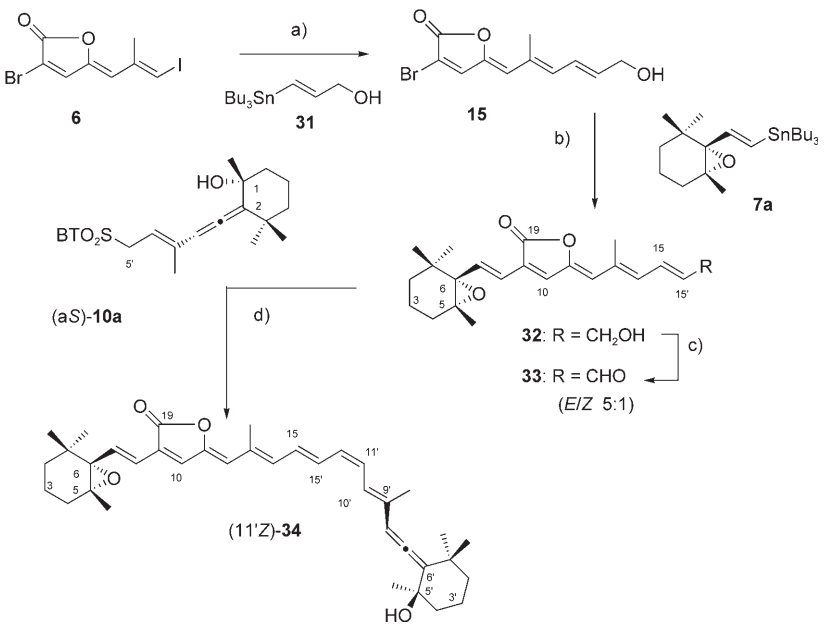
The major isomer of model (a*S*,11′*Z*)-**29a** was used in the second Stille cross-coupling reaction for the final step of the synthesis. The reluctance of alkenylstannane **7a** to engage in Stille cross-coupling reactions made it necessary to considerably increase the reaction temperature to 55 °C and heat the reaction mixture for extended periods (20 h) in order for it to reach completion, even in the presence of the soluble phosphinate salt, with the subsequent reduction of the yield for **30** (21%). Furthermore, although the polyene chain of the starting bromobutenolide **29a** had the 11′*Z* geometry, only the C_{37}-norcarotenoid with the all-*trans* configuration was obtained from the last Stille coupling. The *cis* to *trans* isomerisation of some of the polyene double bonds is facile, as noted in previous approaches to retinoids[41] and carotenoids.[10] Most likely in this case, Pd induces the isomerisation to the most stable carotenoid under the reaction conditions, as we showed that the carotenoid is stable in the absence of palladium (the stability of the precursor of (*Z*)-**29** at room temperature during the first Stille coupling is another proof of this statement). The analysis of the geometry of all the double bonds of the polyene was carried out by studying the similarity between the regions of the vinyl area in the ^{1}H NMR spectra of our model and that of natural peridinin (Scheme 8).

For the natural product, the presence of the hydroxy and acetoxy groups at the C3- and C3′-cyclohexane positions considerably increased the stability of the products and reduced their degradation along the sequence. Heating (a*S*,11′*Z*)-**29d** and alkenylstannane **7b** to 55 °C for 31 h under the same reaction conditions optimized above ($[Pd_2(dba)_3]\cdot CHCl_3$, $[AsPh_3]$, $Bu_4N^+Ph_2PO_2^-$, BHT, THF) provided, after chromatography, a single product in 72% yield. Its structure was assigned as 6′-*epi*-peridinin (6′-*epi*-**1**) by rigorous analysis of coupling constants and 2D HMQC-TOCSY experiments (750 MHz). In addition to the stereoselective coupling reaction, palladium also induced isomerisation of the 11′-*Z*-olefin (peridinin numbering) to the most stable *E* isomer, 6′-*epi*-**1**. This compound has been previously obtained by iodine-assisted photoisomerisation of natural peridinin, after tedious separation of up to eight stereoisomers.[42]

Alternatively, route B required the synthesis of alcohol **15**, the result of the Stille coupling of linchpin **6** and stannane **31**. The precedented Stille cross-coupling between bromobutenolides and organostannanes cocatalyzed by Pd complexes and CuI[39] proved inefficient in our system, and we shifted to the previously optimised conditions, including the soluble phosphinate tin scavenger, for both sequential cross-coupling steps. Regardless of the stannane used, the first coupling takes place at the iodide end of **6**, and **31** furnished allyl alcohol **15** in 68% yield after stirring at ambient temperature for 4.5 h. The second Stille reaction connected bromide **15** and stannane **7a** to produce the polyene **32** in moderate yield (45%), as a consequence of the prolonged heating (50–55 °C, 20 h). Treatment of **32** with TPAP and NMO[43] gave the corresponding aldehyde **33** as a mixture of two geometric isomers (5:1 ratio), which proved to be highly unstable (the yield also decreased considerably at this stage, 36%) and was directly submitted to the final (Sylvestre) Julia olefination with the BT-sulfone (a*S*)-**10a**. Under these mild conditions (-78 to 0 °C, THF), only one isomer of the C_{37}-norcarotenoid was obtained in 63% yield. The analysis of the ^{1}H NMR spectra and their comparison with the reported ^{1}H NMR spectra of peridinin (**1**),[9] allowed us to conclude that the C_{37}-norcarotenoid was the 11′*Z* isomer of

peridinin model (11′*Z*)-**34**. This observation is in agreement with our findings for the $Z>E$ stereoselectivity in the connective olefination reaction of allenyl allyl BT sulfones and unsaturated aldehydes[22] as well as previous reports on similar processes in carotenoids.[9] This polyene proved to be highly labile, as we observed a spontaneous isomerisation at room temperature in favour of the more stable all-*trans* carotenoid **34** (Scheme 9).

From the modelling studies, we concluded that even though route A (Julia-Stille-Stille) directly provided the desired all-*trans* carotenoid by the Pd-induced isomerisation at the last step, route B (Stille-Stille-Julia) affords a double-bond isomer, generated under the milder conditions of the modified Julia condensation in the last step, which is a bonus when the complexity of the polyene is increased. The low yield of the oxidation of polyenol **32** to polyenal **33** was a drawback, but upon further re-evaluation in the context of the synthesis of peridinin, the yield of this step improved, making the alternative routes to carotenoids developed with the model system equally efficient.

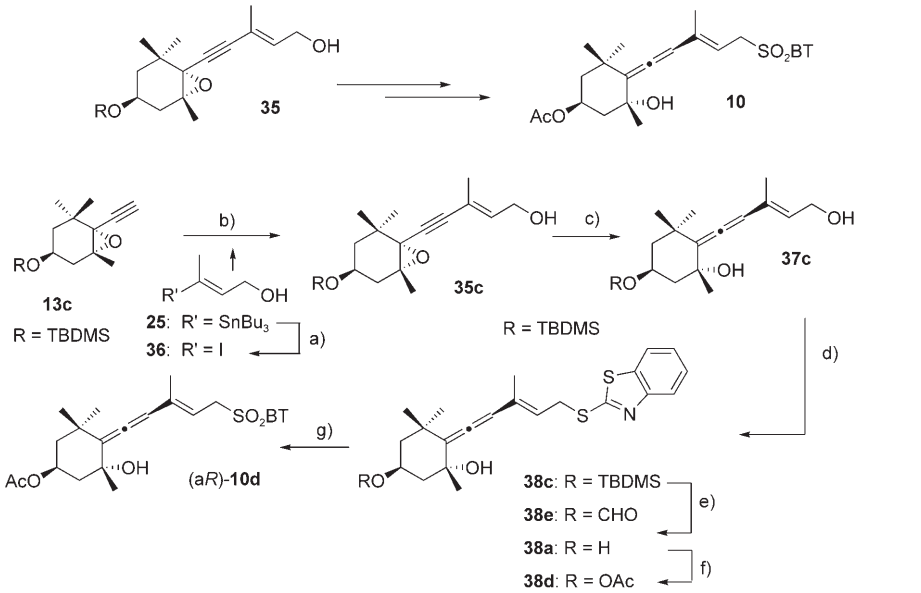


Scheme 9. a) $[Pd_2(dba)_3]\cdot CHCl_3$, $[AsPh_3]$, $Bu_4N^+Ph_2PO_2^-$, THF, 25 °C, 4.5 h (68 %); b) $[Pd_2(dba)_3]\cdot CHCl_3$, $[AsPh_3]$, $Bu_4N^+Ph_2PO_2^-$, THF, 50–55 °C, 20 h (45 %); c) TPAP, NMO, CH_2Cl_2, 25 °C (36 %); d) NaHMDS, THF, −78 °C→0 °C (63 %). TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine *N*-oxide.

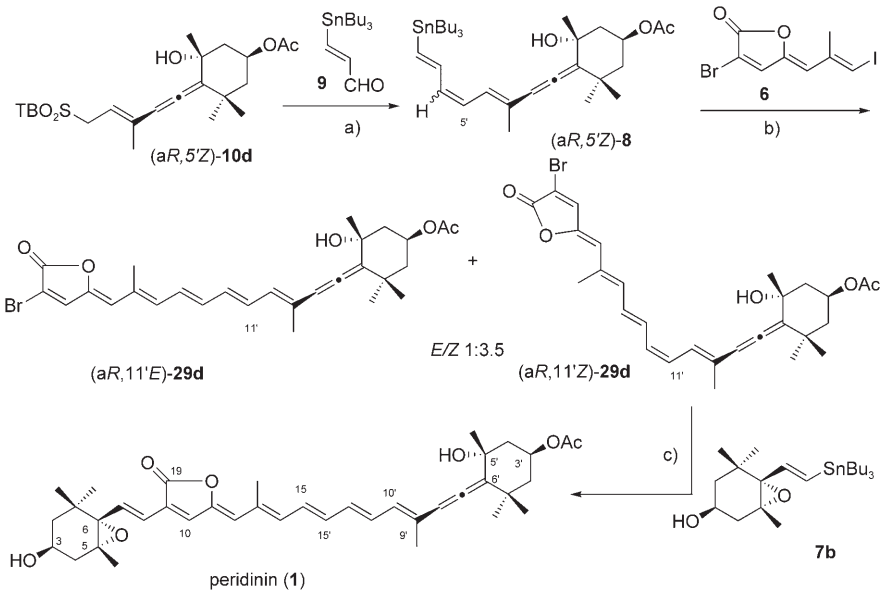
The required alkynyloxirane **35** was derived from a Sonogashira cross-coupling reaction between the protected alkynyloxirane **13c** and iodide **36**,[46] itself obtained from the corresponding organostannane **25** by tin–halogen exchange. Following the optimized conditions developed by Katsumura et al., the use of $[Pd(PPh_3)_4]$ as catalyst and CuI as co-catalyst in diisopropylamine as solvent afforded **35c** from

Synthesis of peridinin

Correction of the allene axis configuration: After many unsuccessful attempts to couple haloallenes and stannanes with retention of configuration,[44] we decided to follow a more classical strategy to prepare the allene axis with the correct a*R* configuration on allenyl allyl BT-sulfone **10** (Scheme 10). This precedented method uses a *syn*-stereospecific S_N2' reduction of the propargyl alcohol in alkynyloxirane **35** with excess DIBAL-H.[45] The high selectivity results from the coordination between aluminium and the epoxide, which directs the hydride to the same face it occupies.



Scheme 10. a) I_2, CH_2Cl_2, 25 °C (98 %); b) $[Pd(PPh_3)_4]$, CuI, $(iPr)_2NH$, 25 °C (78 %); c) DIBAL, CH_2Cl_2, 0 °C (99 %); d) BTSH, DIAD, PPh_3, THF, 0 °C (100 %); e) HCO_2H, THF, H_2O, 25 °C; f) Ac_2O, Py, 25 °C (99 % combined yield); g) 35 % H_2O_2, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, EtOH, −10 °C (93 %). DIBAL = diisobutylaluminium hydride.



Scheme 11. a) NaHMDS, THF, −78 °C (78 %); b) $[Pd_2(dba)_3]$•$CHCl_3$, $[AsPh_3]$, $Bu_4N^+Ph_2PO_2^-$, DMF, 25 °C, 4 h (63 %); c) $[Pd_2(dba)_3]$•$CHCl_3$, $[AsPh_3]$, $Bu_4N^+Ph_2PO_2^-$, THF, 50–55 °C, 19 h (69 %).

13c (78 %, Scheme 10). The stereospecific reduction of the latter with DIBAL-H proceeded quantitatively (100 %) with complete 1,3-chirality transfer. Allenol **37c** was transformed into the corresponding benzothiazolyl allyl sulfide **38c**, by using the Mitsunobu conditions (BTSH, DIAD, PPh_3, THF, 0 °C; 100 %). To avoid the manipulation of more complex structures along the sequence which can easily result in isomerisation, the acetylation at position C3′ was attempted at this stage. Deprotection of the silyl-protecting group was best effected with formic acid (HCO_2H/THF/H_2O, 25 °C),[47] whereas the efficient conditions for acetylation described above (Ac_2O, pyridine, 25 °C; 90 % combined yield), which minimize epimerization of the chiral axis, served well to acquire sulfide **38d** from **38a**. When the reaction is performed on a larger scale, a small amount of the formate byproduct **38e** is isolated. Oxidation of the sulfide with the peroxymolybdate(VI) reagent was carried out at −10 °C to minimize isomerisation of the target sulfone (at higher temperatures, the double bond isomerised to give mixtures of sulfones containing up to 25 % of the *Z* isomer), and afforded in 93 % yield sulfone **10** with the a*R* configuration required for the synthesis of peridinin (**1**).

Completion of the carotenoid skeleton

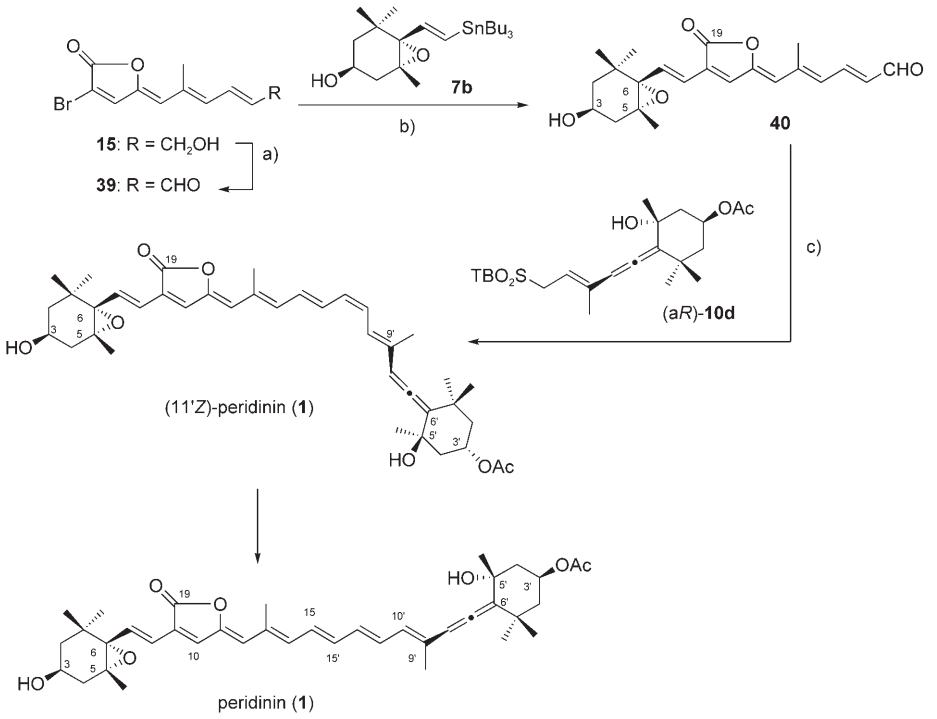
Route A ($C_{11}+C_8+C_{18}$): Modified Julia reaction followed by sequential Stille coupling (and isomerisation under the reaction conditions of the last step)

The sequence, already optimized for the a*S* isomer, worked uneventfully for the components with the correct (a*R*) configuration: the modified Julia reaction furnished the mixture of allenyl trienylstannanes **8** in a 3:1 ratio, which was used as the first organostannane of the sequential Stille coupling reaction with **6** (63 % yield), and the product **29d** was then coupled to **7b** in 69 % yield, delivering peridinin (**1**) with the correct configuration and double-bond geometry (Scheme 11).

Route B: ($C_{15}+C_{11}+C_{11}$): Construction of 11′-*cis*-peridinin and subsequent isomerisation to natural peridinin (**1**) by treatment with palladium.

The coupling of the C_{11}-γ-alkylidenebutenolide central unit for the convergent Stille cross-coupling reaction was attempted at the aldehyde stage to circumvent the low yield of the oxidation of **32** to **33** (Scheme 12). Alcohol **15** (Scheme 12) was oxidized to aldehyde **39** in 72 % yield by treatment of MnO_2 in slightly basic media (Na_2CO_3) to prevent undesired *E*/*Z* isomerisations. The functional-group modification also had an effect on coupling rates to stannane **7b** under our standard conditions, as the γ-alkylidenebutenolide bromide **39** fully conjugated to the aldehyde required an increase in reaction temperature (up to 70 °C) and longer reaction time (26 h). A single product was obtained in 64 % yield, and its all-*trans* structure **40** was assigned after ^{1}H NMR spectroscopic analysis of coupling constants and NOE difference experiments (Scheme 12).

With aldehyde **40** and BT-sulfone (a*R*)-**10** in hand, the crucial (Sylvestre) Julia olefination was explored as the last key step of our synthesis. On the basis of previous results, NaHMDS (THF, −78 °C) was selected to form the stabilized anion of **10**; addition of aldehyde **40** and increase of the temperature to 0 °C enabled the isolation of a major product (53 %) with 11′*Z* geometry (Scheme 12). Isomerization to the desired *trans*-**1** was attempted at ambient temperature in $CDCl_3$ solution, and its evolution was monitored by ^{1}H NMR spectroscopy. After 48 h, a mixture containing an approximately 50:50 ratio of products was obtained. They were separated by HPLC (Develosil C30-UG-5 10/250 NW; MeOH/CH_3CN/Et_3N as eluent, 1 mL min^{-1}) and shown to be the C11′–C14′ isomers, (11′*Z*)-**1** and all-*trans* peridinin (**1**). The geometries of (11′*Z*)-**1** and peridinin (**1**) were confirmed by analysis of coupling constants in their ^{1}H NMR spectra and by ROESY experiments (Figure 3). A more efficient and complete isomerisation was achieved by stirring (11′*Z*)-**1** at ambient temperature for 7 h with the reagents used in the Stille coupling but at a higher loading of Pd/$[AsPh_3]$(1.00:0.13:1.04 molar ratio of polyene/$[Pd_2(dba)_3]$/$[AsPh_3]$), which delivered peridinin (**1**) in 83 % yield.



Scheme 12. a) MnO_2, Na_2CO_3, CH_2Cl_2, 0 °C, 2 h (72 %); b) $[Pd_2(dba)_3]$·$CHCl_3$, $[AsPh_3]$, $Bu_4N^+Ph_2PO_2^-$, DMF, 70 °C, 26 h (64 %); c) NaHMDS, THF, −78 °C to 0 °C (53 %); d) $[Pd_2(dba)_3]$·$CHCl_3$ (0.13 equiv), $[AsPh_3]$ (1.04 equiv), DMF, 25 °C, 7 h (83 %).

Conclusion

Peridinin (**1**), and its 6′-*epi* and 11′*Z* stereoisomers have been stereoselectively prepared by following synthetic routes previously optimised for the preparation of the C3 and C3′-bisdehydroxylated model systems. Highlights of the sequence are the connective modified Julia reaction and sequential Stille coupling using the dihalogenated alkylidenebutenolide **6** as a linchpin. The ordering of the last three steps makes the isolation of the 11′*Z* stereoisomers possible when the modified Julia reaction is employed in the last step. An efficient *Z* to *E* isomerisation of the final carotenoid skeleton uses $[Pd_2(dba)_3]$/$[AsPh_3]$ at ambient temperature, after the observation that the Stille coupling reaction as a last step was accompanied by polyene isomerisation. Another complication of the Stille coupling was found upon reaction of bromoallenes with alkenylstannanes, a process that occurs with inversion of configuration. This called for an alternative synthesis of the allene by using the DIBAL-H-induced reduction of propargyl epoxides. Together these results confirm that the Stille coupling can be used as an efficient synthetic method to construct the carotenoid skeleton, but under the present reaction conditions a limitation on the control of the complete olefin configuration is noted.

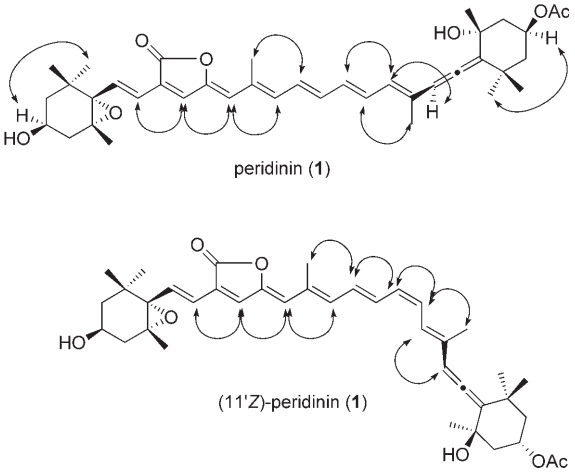


Figure 3. NOEs for peridinin (**1**) and (11′*Z*)-peridinin (**1**) (extracted from their 600 MHz ROESY spectra in $CDCl_3$).

Experimental Section

General: Solvents were dried according to published methods and distilled before use. HPLC-grade solvents were used for the HPLC purification. All other reagents were commercial compounds of the highest purity available. All reactions were carried out under an argon atmosphere, and those not involving aqueous reagents were carried out in oven-dried glassware. Analytical TLC was performed on aluminium plates with Merck Kieselgel $60F_{254}$ and visualised by UV irradiation (254 nm) or by staining with solution of phosphomolibdic acid. Flash-column chromatography was carried out by using Merck Kieselgel 60 (230–400 mesh) under pressure. HPLC was performed by using a Waters instrument with a dualwave detector (254 and 300 nm), preparative Nova Pak HR silica, 60 Å, 19×300 mm and 95:5 hexane/ethyl acetate as the eluent. UV/Vis spectra were recorded on a Cary 100 Bio spectrophotometer by using MeOH as the solvent. IR spectra were obtained on a JASCO IR 4200 spectrophotometer from a thin film deposited onto NaCl glass. Specific rotation was obtained on JASCO P-1020. Mass spectra were obtained on a Hewlett–Packard HP59970 instrument operating at 70 eV by electron ionisation. HRMS were taken on a VG Autospec instrument. ^1H NMR spectra were recorded in $CDCl_3$, C_6D_6 and $(CD_3)_2CO$ at ambient temperature on a Bruker AMX-400 spectrometer at 400 MHz with residual protic solvent as the internal reference ($CDCl_3$, δ_H= 7.26 ppm; C_6D_6, δ_H=7.16 ppm; $(CD_3)_2CO$, δ_H=2.05 ppm); chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The proton spectra are reported as follows: δ (multiplicity, coupling constant J, number of protons, assignment). ^{13}C NMR spectra were recorded in $CDCl_3$, C_6D_6 and $(CD_3)_2CO$ at ambient temperature on the same spectrometer at 100 MHz, with the central peak of $CDCl_3$ (δ_C=77.0 ppm), C_6D_6 (δ_C=128.0 ppm) or $(CD_3)_2CO$ (δ_C=30.8 ppm) as the internal reference. DEPT135 are used to aid in the assignment of signals in the ^{13}C NMR spectra.

(5*S,1′*S**,2′*E*)-3-Bromo-5-[1-hydroxy-3-iodo-2-methyl-propenyl]-5*H*-furan-2-one (19)**: Freshly doubly-distilled chlorotrimethylsilane (1.79 mL, 14.07 mmol) and Et_3N (3.92 mL, 28.14 mmol) were added to a solution of **16** (1.35 g, 8.28 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred for 1 h at 25 °C and the solvent was removed to give **17**. Freshly bidistilled $BF_3{\cdot}OEt_2$ (1.02 mL, 8.28 mmol) and a solution of the mixture obtained above in CH_2Cl_2 (12 mL) were sequentially added to a cooled solution (−78 °C) of **18** (1.62 g, 8.28 mmol) in CH_2Cl_2 (15 mL). After stirring for 1.5 h at −78 °C, a pH 7.1 buffer (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 70:20:10 hexane/EtOAc/CH_2Cl_2) to afford 2.34 g (78 %) of a solid identified as *syn*-**19** and 0.24 g (8 %) of its isomer, *anti*-**19**.

Data for syn-***19***: M.p. 98–100 °C (hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, J = 1.7 Hz, 1H; CH), 6.49 (s, 1H; CH), 5.01 (dd, J = 5.9, 1.7 Hz, 1H; CH), 4.29 (d, J = 5.9 Hz, 1H; CH), 2.62 (br s, 1H; OH), 1.88 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7 (s), 149.1 (d), 144.2 (s), 114.5 (s), 83.6 (d), 82.7 (d), 76.3 (d), 20.7 ppm (q); IR (NaCl): $\tilde{\nu}$ = 3600–3200 (br, OH), 3091 (w), 2919 (w), 1765 (s, C=O), 1608 (w), 1157 cm^{-1} (w); MS (FAB$^+$): *m*/*z* (%): 360 [*M*]$^+$ (7), 359 [*M*]$^+$ (7), 308 (10), 307 (41), 290 (7), 289 (21), 282 (6), 219 (6), 197 (13); HRMS (FAB$^+$): *m*/*z*: calcd for $C_8H_9{}^{79}Br^{127}IO_3$: 358.8780; found: 358.8788; elemental analysis calcd for $C_8H_8BrIO_3$: C 26.77, H 2.25; found: C 26.80, H 2.23.

Data for anti-***19***: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, J = 1.7 Hz, 1H; CH), 6.51 (s, 1H; CH), 4.99 (dd, J = 5.0, 1.7 Hz, 1H; CH), 4.41 (d, J = 5.0 Hz, 1H; CH), 3.24 (br s, 1H; OH), 1.88 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6 (s), 150.1 (d), 144.0 (s), 113.9 (s), 82.8 (d), 82.2 (d), 74.8 (d), 21.1 ppm (q); IR (NaCl): $\tilde{\nu}$ = 3600–3200 (br, OH), 3092 (w, C−H), 2957 (w, C−H), 1775 (s, C=O), 1606 (w), 1057 (m), 1021 (m), 987 cm^{-1} (m); MS (EI$^+$): *m*/*z* (%): 360 [*M*]$^+$ (1), 358 [*M*]$^+$ (1), 198 (4), 197 (100), 162 (6); HRMS (EI$^+$): *m*/*z*: calcd for $C_8H_8{}^{79}Br^{127}IO_3$: 357.8702; found: 357.8704; calcd for $C_8H_8{}^{81}Br^{127}IO_3$: 359.8681; found: 359.8666.

(5*Z*,2′*E*)-3-Bromo-5-(3-iodo-2-methyl-propenyliden)-5*H*-furan-2-one (6): A solution of DIAD (1.10 mL, 5.44 mmol) was added to a cooled (−50 °C) solution of *syn*-**19** (0.65 g, 1.81 mmol) and PPh_3 (1.43 g, 5.44 mmol) in THF (17 mL). The mixture was stirred for 3.5 h, allowing the temperature to rise to 0 °C smoothly. After this time, water was added and the mixture was extracted with CH_2Cl_2 (×3). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 90:10 hexane/EtOAc) to afford 0.35 g (57 %) of a yellow solid identified as (*Z*)-**6** and 0.05 g (8 %) of a yellow solid identified as (*E*)-**6** in a 7:1 *Z*/*E* ratio.

*Data for (*Z*)-**6***: M.p. 87–88 °C (CH_2Cl_2/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1H; CH), 6.97 (s, 1H; CH), 5.73 (s, 1H; CH), 2.21 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1 (s), 144.9 (s), 142.5 (d), 142.0 (s), 114.5 (d), 111.6 (s), 93.1 (d), 22.9 ppm (q); IR (NaCl): $\tilde{\nu}$ = 3053 (w, C−H), 2924 (w, C−H), 2854 (w, C−H), 1780 (s, C=O), 975 cm^{-1} (m); UV (MeOH): λ_{max} = 343 nm; MS (FAB$^+$): *m*/*z* (%): 343 [*M*]$^+$ (2), 342 (2), 341 [*M*]$^+$ (2), 340 (1), 292 (3), 274 (2), 258 (1), 257 (2); HRMS (FAB$^+$): *m*/*z*: calcd for $C_8H_7{}^{81}Br^{127}IO_2$: 342.8654; found: 342.8658; elemental analysis calcd for $C_8H_6BrIO_2$: C 28.18, H 1.77; found: C 28.00, H 1.73.

*Data for (*E*)-**6***: M.p: 107–108 °C (CH_2Cl_2/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1H; CH), 6.80 (d, J = 0.9 Hz, 1H; CH), 6.36 (s, 1H; CH), 2.10 ppm (d, J = 0.9 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4 (s), 146.9 (s), 141.0 (s), 138.2 (d), 117.0 (d), 114.8 (s), 91.4 (d), 23.0 ppm (q); IR (NaCl): $\tilde{\nu}$ = 2922 (w, C−H), 2853 (w, C−H), 1749 cm^{-1} (s, C=O); UV (MeOH): λ_{max} = 346 nm; MS (FAB$^+$): *m*/*z* (%): 323 (30), 322 (100), 282 (42), 279 (16), 251 (16), 250 (34), 210 (18), 193 (17), 191 (18), 167 (60), 165 (27); HRMS (FAB$^+$): *m*/*z*: calcd for $C_8H_7{}^{79}Br^{127}IO_2$: 340.8674; found: 340.8689; elemental analysis calcd for $C_8H_6BrIO_2$: C 28.18, H 1.77; found: C 28.61, H 1.77.

(−)-[(*R*)-4-(*tert*-Butyldimethylsilyloxy)-2,6,6-trimethylcyclohex-1-enyl]-methanol (21c): A cooled (−78 °C) solution of **20** (1.0 g, 2.63 mmol) in THF (3 mL) was treated with *t*BuLi (3.25 mL, 1.7 M in pentane, 5.52 mmol) and a solution of paraformaldehyde (0.12 g, 3.94 mmol) in THF (2 mL) was added. After stirring for 1 h at −78 °C and 15 h at 25 °C, brine was slowly added and the mixture was extracted with *t*BuOMe (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 80:20 hexane/EtOAc) to afford 1.59 g (71 %) of a white solid identified as **21c**. $[\alpha]_D^{25}$ = −109.2 (c = 0.03 in $CHCl_3$); m.p. 69–71 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.11 (d, J = 11.4 Hz, 1H; CH_2), 4.03 (d, J = 11.4 Hz, 1H; CH_2), 3.88 (m, 1H; CH_2), 2.11 (m, 1H; CH_2), 2.00 (dd, J = 17.0, 9.4 Hz, 1H; CH_2), 1.71 (s, 3H; CH_3), 1.59 (ddd, J = 12.3, 3.3, 2.0 Hz, 1H; CH_2), 1.43 (t, J = 12.1 Hz, 1H; CH_2), 1.05 (s, 3H; CH_3), 1.01 (s, 3H; CH_3), 0.85 (s, 9H; CH_3), 0.03 ppm (s, 6H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1 (s), 131.2 (s), 65.5 (d), 58.2 (t), 48.4 (t), 42.6 (t), 36.6 (s), 29.3 (q), 28.4 (q), 25.8 (q, 3×), 19.4 (q), 18.1 (s), −4.7 ppm (q, 2×); IR (NaCl): $\tilde{\nu}$ = 3600–3100 (br, OH), 2926 (s, C−H), 2857 (s, C−H), 1465 (m), 1382 (m), 1253 (s), 1087 cm^{-1} (s); MS (EI$^+$): *m*/*z* (%): 209 (23), 135 (45), 119 (59), 109 (19), 107 (27), 105 (15), 93 (27), 91 (42), 77 (17), 75 (100), 73 (57), 67 (19); HRMS (EI$^+$): *m*/*z*: calcd for $C_{16}H_{30}OSi$: 266.2066; found: 266.2065; elemental analysis calcd for $C_{16}H_{32}O_2Si$: C 67.54, H 11.34; found: C 67.54, H 11.52.

(+)-[(1*R*,6*R*)-2,2,6-Trimethyl-7-oxa-bicyclo[4.1.0]heptan-1-yl]methanol (22a). General procedure for the Sharpless asymmetric epoxidation: Ti(O*i*Pr)$_4$ (3.71 mL, 12.57 mmol) was added to a cooled (−20 °C) solution of (−)-D-DET (2.59 mL, 15.09 mmol) in CH_2Cl_2 (35 mL) containing 4 Å molecular sieves. After stirring for 10 min, a solution of TBHP (5.4 mL, 4.63 M in *iso*-octane, 25.15 mmol) was added and the mixture was stirred for 30 min at −20 °C. A solution of β-cyclogeraniol **21a** (1.9 g, 12.57 mmol) in CH_2Cl_2 (10 mL) was added and stirred for 12 h. The mixture was diluted with *t*BuOMe (30 mL) at −20 °C and a 30 % aqueous solution of NaOH (1 mL) and brine (1 mL) were added. The resulting mixture was warmed up to room temperature, Na_2SO_4 and Celite were added and the mixture was filtered and extracted thoroughly with *t*BuOMe. The combined organics layers were dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (silica gel, 80:20 hexane/EtOAc) to afford 2.1 g (98 %) of a colourless oil identified as **22a**. $[\alpha]_D^{20}$ = +46.08 (c = 0.08 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (dd, J = 11.3, 5.0 Hz, 1H; CH_2), 3.64 (dd, J = 11.3, 5.0 Hz, 1H; CH_2), 1.90–1.80 (m, 2H; CH_2), 1.80–1.70 (m, 1H; CH_2), 1.40–1.30 (m, 3H; CH_2), 1.33 (s, 3H; CH_3), 1.01 (s, 3H; CH_3), 0.99 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.9 (s), 64.6 (s), 58.8 (t), 36.5 (t), 32.8 (s), 31.0 (t), 25.0 (q), 24.1 (q), 20.6 (q), 17.0 ppm (t); IR (NaCl): $\tilde{\nu}$ = 3700–3200 (br, OH), 2940 (s, C−H), 1455 (s), 1035 cm^{-1} (s); MS (EI$^+$): *m*/*z* (%): 139 [*M*−CH_2OH]$^+$ (6), 137 (10), 111 (25), 109 (35), 97 (10), 97 (21), 95 (28), 86 (100), 85 (82), 84 (32), 83 (17), 82 (21), 81 (16), 79 (26), 71 (71), 70 (16), 69 (48), 67 (30); HRMS (EI$^+$): *m*/*z*: calcd for $C_{10}H_{18}O_2$: 170.1302; found: 170.1306.

(−)-[(1*R*,4*S*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptan-1-yl]methanol (22c): Following the general procedure for the Sharpless asymmetric epoxidation, the reaction of (−)-D-DET (0.44 mL, 2.53 mmol), Ti(O*i*Pr)$_4$ (0.62 mL, 2.11 mmol), TBHP (0.90 mL, 4.69 M in *iso*-octane, 4.22 mmol) and **21c** (0.60 g, 2.11 mmol) in CH_2Cl_2 (8 mL) afforded, after purification by column chromatography (silica gel, 85:15→50:50 hexane/EtOAc), 0.62 g (98 %) of a colourless oil identified as **22c**. $[\alpha]_D^{29}$ = −44.4 (c = 0.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80–3.60 (m, 3H; CH + CH_2), 2.19 (dd, J = 14.2, 4.2 Hz, 1H; CH_2), 1.76 (m, 1H; OH), 1.60 (dd, J = 14.1, 8.8 Hz, 1H; CH_2), 1.39 (m, 1H; CH_2), 1.37 (s, 3H; CH_3), 1.21 (dd, J = 13.2, 2.5 Hz, 1H; CH_2), 1.10 (s, 3H; CH_3), 1.03 (s, 3H; CH_3), 0.84 (s, 9H; CH_3), 0.01 ppm (s, 6H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.1 (s), 65.6 (s), 64.2 (d), 59.7 (t), 47.9 (t), 42.2 (t), 34.0 (s), 26.9 (q), 25.7 (q, 3×), 24.7 (q), 19.6 (q), 18.0 (s), −4.8 ppm (q, 2×); IR (NaCl): $\tilde{\nu}$ = 3600–3100 (br, OH), 2959 (s, C−H), 2931 (s, C−H), 2857 (s, C−H), 1468 (m), 1383 (m), 1254 (s), 1088 cm^{-1} (s); MS (EI$^+$): *m*/*z* (%): 225 (87), 211 (48), 185 (70), 171 (70), 169 (86), 157 (90), 151 (54), 143 (67), 141 (55), 133 (45), 121 (55), 119 (59), 111 (64), 109 (81), 107 (64), 105 (56), 101 (41), 95 (40), 93 (62), 91 (67), 84 (40), 83 (68), 76 (95), 75 (100), 73 (98); HRMS (EI$^+$): *m*/*z*: calcd for $C_{12}H_{23}O_3Si$: 243.1416 [*M*−*t*Bu]$^+$; found: 243.1413.

(−)-(1*S*,6*R*)-2,2,6-Trimethyl-7-oxabicyclo[4.1.0]heptane-1-carbaldehyde (23a). General procedure for the Swern oxidation: DMSO (1.32 mL, 18.57 mmol) was added to a cooled (−60 °C) solution of oxalyl chloride (0.95 mL, 10.83 mmol) in CH_2Cl_2 (23 mL), and the mixture was stirred for 5 min. A solution of **22a** (1.32 g, 7.74 mmol) in CH_2Cl_2 (23 mL) was added and the mixture was stirred for 15 min. Finally, Et_3N (7.12 mL, 51.08 mmol) was added and after 10 min, the mixture was warmed to room temperature. The mixture was poured over H_2O and extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 95:5 hexane/EtOAc) to afford 1.15 g (89%) of a colourless oil identified as **23a**. $[\alpha]_D^{23} = -18.4$ ($c = 0.08$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.73$ (s, 1H; CH), 1.91 (m, 1H; CH_2), 1.75 (m, 1H; CH_2), 1.45 (m, 4H; CH_2), 1.31 (s, 3H; CH_3), 1.27 (s, 3H; CH_3), 1.05 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 201.7$ (d), 73.1 (s), 65.2 (s), 35.3 (t), 32.5 (s), 29.3 (t), 26.0 (q), 24.4 (q), 21.3 (q), 16.7 ppm (t); IR (NaCl): $\tilde{\nu} = 2940$ (s, C−H), 1713 (s, C=O), 1460 cm^{-1} (m); MS (EI$^+$): m/z (%): 139 $[M-CHO]^+$ (24), 125 (15), 111 (20), 110 (19), 109 (16), 107 (10), 95 (36), 91 (10), 84 (12), 83 (12), 82 (29), 81 (17), 79 (11), 71 (43), 70 (25), 67 (20); HRMS (EI$^+$): m/z: calcd for $C_{10}H_{16}O_2$: 168.1150; found: 168.1157.

(−)-(1*S*,4*S*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptane-1-carbaldehyde (23c): Following the general procedure for the Swern oxidation, the reaction of oxalyl chloride (0.46 mL, 5.27 mmol), DMSO (0.64 mL, 9.04 mmol), **22c** (1.13 g, 3.77 mmol) and Et_3N (3.5 mL, 24.86 mmol) in CH_2Cl_2 (24 mL) afforded, after purification by column chromatography (silica gel, 95:5 hexane/EtOAc), 1.02 g (91%) of a colourless oil identified as **23c**. $[\alpha]_D^{29} = -97.2$ ($c = 0.04$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.76$ (s, 1H; CH), 3.90–3.80 (m, 1H; CH_2), 2.20 (dd, $J = 14.8$, 5.1 Hz, 1H; CH_2), 1.67 (dd, $J = 14.8$, 7.4 Hz, 1H; CH_2), 1.45 (dd, $J = 13.3$, 3.0 Hz, 1H; CH_2), 1.34 (s, 3H; CH_3), 1.30–1.20 (m, 1H; CH_2), 1.24 (s, 3H; CH_3), 1.03 (s, 3H; CH_3), 0.84 (s, 9H; CH_3), 0.01 ppm (s, 6H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 200.3$ (d), 72.2 (s), 66.1 (s), 64.1 (d), 46.2 (t), 40.7 (t), 33.5 (s), 27.9 (q), 26.1 (q), 25.7 (q, 3×), 20.5 (q), 17.9 (s), −4.9 ppm (q, 2×); IR (NaCl): $\tilde{\nu} = 2931$ (s, C−H), 2857 (s, C−H), 1728 (s, C=O), 1469 (m), 1386 (m), 1255 (s), 1089 cm^{-1} (s); MS (EI$^+$): m/z (%): 225 (9), 171 (9), 169 (16), 157 (29), 155 (12), 143 (9), 123 (10), 121 (14), 109 (16), 101 (12), 93 (11), 91 (10), 75 (100), 73 (28); HRMS (EI$^+$): m/z: calcd for $C_{12}H_{21}O_3Si$: 241.1260 $[M-t\text{Bu}]^+$; found: 241.1245.

(+)-(1*R*,6*R*)-1-Ethynyl-2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptane (13a). General procedure for the Colvin reaction: A cooled (0 °C) solution of $i\text{Pr}_2\text{NH}$ (0.59 mL, 4.18 mmol) in THF (30 mL) was treated with *n*BuLi (3.89 mL, 1.23 M in hexane, 4.78 mmol) and then stirred for 30 min. The mixture was cooled down to −78 °C and trimethylsilyldiazomethane (2.09 mL, 2.0 M in THF, 4.18 mmol) was added. After stirring for 30 min, a solution of **23a** (0.50 g, 2.98 mmol) in THF (15 mL) was added and the resulting mixture was stirred for 1 h at −78 °C and for 2 h at 25 °C. The mixture was poured over ice-water and extracted with Et_2O (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 98:2 hexane/EtOAc) to afford 0.412 g (84%) of a yellow oil identified as **13a**. $[\alpha]_D^{22} = +25.51$ ($c = 0.09$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 2.36 (s, 1H; CH), 1.80–1.70 (m, 1H; CH_2), 1.70–1.60 (m, 1H; CH_2), 1.46 (s, 3H; CH_3), 1.40–1.30 (m, 2H; CH_2), 1.16 (s, 3H; CH_3), 1.13 (s, 3H; CH_3), 1.00–0.90 ppm (m, 2H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 81.2 (s), 73.4 (d), 64.8 (s), 63.9 (s), 33.8 (t), 33.2 (s), 28.9 (t), 26.1 (q), 25.4 (q), 22.7 (q), 16.7 ppm (t); IR (NaCl): $\tilde{\nu} = 3310$ (s, C=C−H), 3000–2800 (s, C−H), 2045 (w, C=C), 1460 cm^{-1}; MS (EI$^+$): m/z (%): 164 $[M]^+$ (1), 149 (16), 121 (23), 107 (11), 106 (22), 105 (27), 93 (16), 91 (100), 79 (17), 77 (19), 73 (13); HRMS (EI$^+$): m/z: calcd for $C_{11}H_{16}O$: 164.1201; found: 164.1208.

(−)-*tert*-Butyldimethylsilyl (1*R*,3*S*,6*R*)-6-ethynyl-1,5,5-trimethyl-7-oxabicyclo[4.1.0]heptan-3-yl ether (13c): Following the general procedure for Colvin reaction, the reaction of $i\text{Pr}_2\text{NH}$ (2.23 mL, 15.89 mmol) in THF (90 mL), *n*BuLi (11.8 mL, 1.54 M in hexane, 18.14 mmol), trimethylsilyldiazomethane (8.0 mL, 2.0 M in THF, 15.89 mmol) and **23c** (3.38 g, 11.34 mmol) in THF (48 mL) afforded, after purification by column chromatography (silica gel, 100:0→99:1 hexane/EtOAc), 3.10 g (92%) of a yellow oil identified as **13c**. $[\alpha]_D^{29} = -119.8$ ($c = 0.02$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.80$–3.70 (m, 1H; CH), 2.35 (s, 1H; CH_2), 2.18 (ddd, $J = 14.5$, 5.1, 1.5 Hz, 1H; CH_2), 1.62 (dd, $J = 14.5$, 7.9 Hz, 1H; CH_2), 1.46 (s, 3H; CH_3), 1.50–1.40 (m, 1H; CH_2), 1.22 (s, 3H; CH_3), 1.20–1.10 (m, 1H; CH_2), 1.07 (s, 3H; CH_3), 0.83 (s, 9H; CH_3), −0.01 ppm (s, 6H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 80.7$ (s), 73.8 (d), 66.2 (s), 64.1 (d), 63.0 (s), 45.4 (t), 40.1 (t), 33.7 (s), 29.4 (q), 25.7 (q, 3×), 25.4 (q), 21.5 (q), 17.9 (s), −4.9 ppm (q, 2×); IR (NaCl): $\tilde{\nu} = 3311$ (m, C≡C-H), 2957 (s, C−H), 2931 (s, C−H), 2857 (m, C−H), 2100 (w, C≡C), 1469 (m), 1385 (m), 1364 (m), 1255 (s), 1085 cm^{-1} (s); MS (EI$^+$): m/z (%): 237 (2), 181 (73), 165 (64), 143 (86), 121 (84), 115 (84), 105 (16), 101 (18), 93 (52), 91 (17), 77 (29), 75 (100), 73 (83); HRMS (EI$^+$): m/z: calcd for $C_{13}H_{21}O_2Si$: 237.1311 $[M-t\text{Bu}]^+$; found: 237.1321.

(−)-(1*R*,3*S*,6*R*)-6-Ethynyl-1,5,5-trimethyl-7-oxabicyclo[4.1.0]heptan-3-ol (13b): A solution of **13c** (1.62 g, 5.49 mmol) in THF (10 mL) was treated with $n\text{Bu}_4\text{NF}$ (10.97 mL, 1 M in THF, 10.97 mmol). After stirring for 2 h, the mixture was poured over a saturated aqueous $NaHCO_3$ solution and extracted with Et_2O (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 85:15 hexane/EtOAc) to afford 0.84 g (85%) of a white solid identified as **13b**. $[\alpha]_D^{24} = -76.0$ ($c = 0.05$ in $CHCl_3$); m.p. 70–73 °C (hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.78$ (dddd, $J = 10.2$, 8.6, 5.0, 3.5 Hz, 1H; CH_2), 2.37 (s, 1H; CH), 2.32 (dd, $J = 14.3$, 5.1 Hz, 1H; CH_2), 1.59 (dd, $J = 14.3$, 8.6 Hz, 1H; CH_2), 1.55 (ddd, $J = 13.1$, 3.4, 1.8 Hz, 1H; CH_2), 1.48 (s, 3H; CH_3), 1.24 (s, 3H; CH_3), 1.19 (ddd, $J = 13.3$, 10.4, 2.9 Hz, 1H; CH_2), 1.09 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 80.4$ (s), 74.0 (d), 66.4 (s), 63.6 (d), 62.9 (s), 45.6 (t), 39.6 (t), 33.9 (s), 29.6 (q), 25.3(q), 21.3 ppm (q); IR (NaCl): $\tilde{\nu} = 3600$–3100 (br, OH), 3292 (s, C≡C−H), 2963 (s, C−H), 2930 (s, C−H), 2100 (w, C≡C), 1461 (m), 1108 (s), 1051 cm^{-1} (s); MS (EI$^+$): m/z (%): 180 $[M]^+$ (8), 179 $[M-1]^+$ (10), 136 (28), 122 (15), 121 (100), 119 (17), 107 (17), 96 (40), 95 (17), 94 (16), 93 (65), 91 (26), 80 (19), 79 (63), 77 (37), 69 (16); HRMS (FAB$^+$): m/z: calcd for $C_{11}H_{16}O_2$: 180.1150; found: 180.1158; elemental analysis calcd for $C_{11}H_{16}O_2$: C 73.30, H 8.95; found: C 73.28, H 9.12.

(−)-Tributyl{(1*E*,1′*S*,6′*R*)-2-(2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptan-1-yl)vinyl}stannane (7a). General procedure for stannylation catalyzed by palladium: $[PdCl_2(PPh_3)_2]$ (0.02 g, 0.03 mmol) and $n\text{Bu}_3\text{SnH}$ (0.52 mL, 1.97 mmol) were sequentially added to a solution of **13a** (0.27 g, 1.64 mmol) in THF (9 mL). After stirring for 10 min at 25 °C, the mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel C-18, 70:30 CH_3CN/CH_2Cl_2) to afford 0.52 g (70%) of a yellow oil identified as **7a**. $[\alpha]_D^{23} = -19.42$ ($c = 0.59$ in $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 6.61$ (d, $J = 19.1$, $^2J(\text{Sn,H}) = 81.1$ Hz, 1H; CH), 6.39 (d, $J = 19.1$, $^3J(\text{Sn,H}) = 65.5$ Hz, 1H; CH), 1.90–1.80 (m, 1H; CH_2), 1.70–1.50 (m, 9H; CH_2), 1.50–1.20 (m, 7H; CH_2), 1.22 (s, 3H; CH_3), 1.16 (s, 3H; CH_3), 1.10 (s, 3H; CH_3), 1.10–0.90 ppm (m, 15H; $CH_2 + CH_3$); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 144.0$ (d), 131.5 (d), 72.8 (s), 64.2 (s), 36.3 (t), 33.6 (s), 30.4 (t), 29.6 (t 3×, $^3J(\text{Sn,H}) = 20.9$ Hz), 27.6 (t 3×, $^2J(\text{Sn,H}) = 51.4$ Hz), 26.3 (q), 26.1 (q), 21.3 (q), 17.6 (t), 13.9 (q, 3×), 9.9 ppm (t 3×, $^1J(\text{Sn,H}) = 334.1$ Hz); IR (NaCl): $\tilde{\nu} = 2957$ (s, C−H), 2925 (s, C−H), 2871 (s, C−H), 1460 (m), 1377 cm^{-1} (w); MS (FAB$^+$): m/z (%): 403 (15), 401 (16), 400 (100), 398 (40), 397 (78), 396 (32), 395 (43), 291 (24), 289 (19), 287 (13), 235 (11), 179 (24), 177 (29), 175 (20), 165 (24); HRMS (FAB$^+$): m/z: calcd for $C_{23}H_{45}O^{120}Sn$: 457.2492; found: 457.2482.

(−)-(1*R*,3*S*,6*S*,1′*E*)-6-[2-(Tributyltin)vinyl]-1,5,5-trimethyl-7-oxabicyclo-[4.1.0]heptan-3-ol (7b): Following the general procedure for stannylation catalyzed by palladium, the reaction of **13b** (0.20 g, 1.13 mmol), $[PdCl_2(PPh_3)_2]$ (0.015 g, 0.02 mmol) and $n\text{Bu}_3\text{SnH}$ (0.36 mL, 1.35 mmol) in THF (6 mL) afforded, after purification by column chromatography (silica gel C-18, CH_3CN), 0.36 g (68%) of a colourless oil identified as **7b**. $[\alpha]_D^{26} = -83.9$ ($c = 0.05$ in $CHCl_3$); ^{1}H NMR (400 MHz, $(CD_3)_2CO$): $\delta = 6.29$ (d, $J = 19.1$ Hz, 1H; CH), 6.19 (d, $J = 19.1$ Hz, 1H; CH), 3.71 (m, 1H; CH), 3.43 (d, $J = 4.6$ Hz, 1H; OH), 2.21 (ddd, $J = 14.2$, 5.0, 1.7 Hz, 1H; CH_2), 1.60–1.50 (m, 8H; CH_2), 1.40–1.30 (m, 6H; CH_2), 1.20 (m, 1H; CH_2), 1.13 (s, 6H; CH_3), 1.00–0.80 (m, 15H; $CH_2 + CH_3$), 0.88 ppm (s, 3H;

CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta = 146.0$ (d), 132.4 (d), 73.3 (s), 67.4 (s), 64.8 (d), 49.0 (t), 42.8 (t), 36.3 (s), 30.9 (q), 30.7 (t), 28.9 (t), 26.3 (q), 21.4 (q), 15.0 (q), 11.1 ppm (t); IR (NaCl): $\tilde{\nu} = 3600$–3100 (br, OH), 2957 (s, C–H), 2924 (s, C–H), 2852 (m, C–H), 1594 (w), 1160, 1325, 1049 cm^{-1}; MS (FAB^+): *m/z* (%): 419 (15), 417 (15), 416 (19), 415 (100), 414 (40), 413 (78), 412 (32), 411 (43), 357 (18), 291 (33), 289 (26), 179 (45), 177 (57), 176 (18), 175 (39); HRMS (FAB^+): *m/z*: calcd for $C_{23}H_{43}O_2{}^{118}Sn$: 469.2279; found: 469.2279.

(−)-(1*R*,2a*R*)-2-(2-Bromovinyliden)-1,3,3-trimethylcyclohexanol (12a). General procedure for bromoallene formation: CuBr (0.34 g, 2.36 mmol), NH_4Br (0.12 g, 1.18 mmol) and HBr (48% aq., 0.43 mL, 3.78 mmol) were added sequentially to a cooled (−10 °C) solution of **13a** (0.39 g, 2.36 mmol) in Et_2O (11.5 mL). After stirring for 30 min, an aqueous solution of NH_4Cl/NH_3 1:1 (10 mL) was added and the layers were separated. The organic layer was washed with brine (3×), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 85:15 hexane/EtOAc) to afford 0.501 g (86%) of a white solid identified as **12a**. $[\alpha]_D^{22} = -17.78$ ($c = 0.146$ in $CHCl_3$); m.p. 47–49 °C (pentane); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.96$ (s, 1H; CH), 1.90–1.70 (m, 2H; CH_2), 1.51 (m, 3H; CH_2), 1.43 (m, 1H; CH_2), 1.37 (s, 3H; CH_3), 1.24 (s, 3H; CH_3), 1.09 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.9$ (s), 126.7 (s), 74.1 (d), 70.5 (s), 40.0 (t, 2×), 34.9 (s), 30.8 (q), 30.6 (q), 29.0 (q), 18.0 ppm (t); IR (NaCl): $\tilde{\nu} = 3600$–3200 (br, OH), 2960 (s, C–H), 2928 (s, C–H), 2868 (m, C–H), 1945 (w, C=C=C), 1454 (m), 1144 cm^{-1} (s); MS (EI^+): *m/z* (%): 246 $[M(^{81}Br)]^+$ (2), 244 $[M(^{79}Br)]^+$ (2), 231 (14), 229 (14), 166 (11), 165 (88), 162 (28), 160 (27), 151 (42), 147 (16), 123 (29), 122 (12), 121 (38), 109 (37), 109 (27), 108 (10), 107 (100), 105 (20), 93 (23), 91 (39), 85 (11), 84 (17), 81 (25), 80 (19), 79 (37), 77 (26), 71 (28), 69 (47), 65 (11); HRMS (EI^+): *m/z*: calcd for $C_{11}H_{17}{}^{79}BrO$: 244.0463; found: 244.0457; elemental analysis calcd for $C_{11}H_{17}BrO$: C 53.89, H 6.99; found: C 53.80, H 7.08.

(−)-(1*R*,3*S*,6a*R*)-6-(2-Bromovinyliden)-1,5,5-trimethylcyclohexane-1,3-diol (12b): Following the general procedure for bromoallene formation, the reaction of **13b** (0.20 g, 1.11 mmol), CuBr (0.16 g, 1.11 mmol), NH_4Br (0.06 g, 0.56 mmol) and HBr (48% ac, 0.20 mL, 1.78 mmol) in Et_2O (5.0 mL) for 2.5 h at 25 °C afforded, after purification by column chromatography (silica gel, 60:40→40:60 hexane/EtOAc), 0.25 g (85%) of a colourless oil identified as **12b**. $[\alpha]_D^{24} = -59.0$ ($c = 0.02$ in $CHCl_3$); m.p. 134–135 °C (hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.95$ (s, 1H; CH), 4.25 (tt, $J = 11.4$, 4.1 Hz, 1H; CH), 2.20 (ddd, $J = 13.4$, 4.1, 2.4 Hz, 1H; CH_2), 1.88 (ddd, $J = 12.5$, 4.1, 2.4 Hz, 1H; CH_2), 1.39 (t, $J = 11.6$ Hz, 1H; CH_2), 1.39 (s, 3H; CH_3), 1.31 (t, $J = 11.9$ Hz, 1H; CH_2), 1.29 (s, 3H; CH_3), 1.12 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.4$ (s), 124.2 (s), 74.2 (d), 72.3 (s), 63.8 (d), 48.7 (t), 48.4 (t), 35.9 (s), 31.3 (q), 30.6 (q), 29.4 ppm (q); IR (NaCl): $\tilde{\nu} = 3600$–3100 (br, OH), 2927 (s, C–H), 1950 (w, C=C=C), 1458 (m), 1152 (s), 1041 cm^{-1} (s); MS (EI^+): *m/z* (%): 182 (13), 181 (100), 163 (36), 160 (76), 158 (69), 139 (12), 125 (17), 123 (83), 122 (12), 121 (35), 107 (24), 105 (35), 95 (18), 91 (14), 87 (22), 85 (11), 83 (29), 81 (20), 80 (11), 79 (42), 77 (43); HRMS (EI^+): *m/z*: calcd for $C_{11}H_{17}{}^{79}BrO_2$: 260.0412; found: 260.0418; elemental analysis calcd for $C_{11}H_{17}BrO_2$: C 50.59, H 6.56; found: C 50.86; H 6.63.

(−)-(1*S*,3*R*,4a*R*)-4-(2-Bromovinyliden)-3-hydroxy-3,5,5-trimethylcyclohexyl acetate (12d): Ac_2O (2.10 mL, 22.37 mmol) was added to a solution of **12b** (1.16 g, 4.47 mmol) in pyridine (14 mL). After stirring for 3 h, the mixture was extracted with *t*BuOMe (3×). The combined organic layers were washed with a saturated aqueous $CuSO_4$ solution (2×), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 90:10→80:20 hexane/EtOAc) to afford 1.15 g (85%) of a white solid identified as **12d**. $[\alpha]_D^{24} = -35.7$ ($c = 0.03$ in $CHCl_3$); m.p. 94–96 °C (hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.95$ (s, 1H; CH), 5.28 (m, 1H; CH), 2.20 (ddd, $J = 13.0$, 4.1, 2.3 Hz, 1H; CH_2), 1.98 (s, 3H; CH_3), 1.90 (ddd, $J = 12.4$, 4.1, 2.3 Hz, 1H; CH_2), 1.50–1.30 (m, 2H; CH_2), 1.38 (s, 3H; CH_3), 1.32 (s, 3H; CH_3), 1.11 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.3$ (s), 170.4 (s), 123.7 (s), 74.2 (d), 71.8 (s), 67.4 (d), 44.6 (t, 2×), 35.7 (s), 31.1 (q), 30.3 (q), 29.0 (q), 21.2 ppm (q); IR (NaCl): $\tilde{\nu} = 3600$–3100 (br, OH), 3058 (w, C–H), 2966 (s, C–H), 2927 (s, C–H), 2859 (m, C–H), 1949 (w, C=C=C), 1720 (s, C=O), 1366 (s), 1267 (s, C–O), 1031 cm^{-1} (s); MS (EI^+): *m/z* (%): 304 $[M]^+$ (4), 302 $[M]^+$ (3), 186 (17), 163 (100), 160 (50), 158 (40), 121 (32), 107 (21), 105 (46), 91 (16), 84 (38), 81 (15), 79 (24), 77 (27), 69 (18); HRMS (EI^+): *m/z*: calcd for $C_{13}H_{19}{}^{79}BrO_3$: 302.0518; found: 302.0528; calcd for $C_{13}H_{19}{}^{81}BrO_3$: 304.0497; found: 304.0498; elemental analysis calcd for $C_{13}H_{19}BrO_3$: C 51.50; H 6.32; found: C 51.32; H 6.35.

(*E*)-1-(Benzothiazol-2-yl)sulfanyl-3-(tri-*n*-butyltin)-3-methylprop-2-ene (26). General procedure for sulfide formation: A solution of **25** (4.37 g, 12.12 mmol), 2-mercaptobenzothiazol (3.04 g, 18.19 mmol) and PPh_3 (5.08 g, 19.40 mmol) in THF (65 mL) was stirred for 5 min at 0 °C. A solution of DIAD (3.52 mL, 18.19 mmol) in THF (22 mL) was added and the mixture was stirred for 30 min at 25 °C. The solvent was removed and the residue was purified by column chromatography (silica gel, 96:2:2 hexane/EtOAc/Et_3N) to afford 6.07 g (98%) of a colourless oil identified as **26**. ^1H NMR (400 MHz, C_6D_6): $\delta = 7.90$ (d, $J = 8.2$ Hz, 1H; ArH), 7.23 (d, $J = 8.0$ Hz, 1H; ArH), 7.08 (t, $J = 8.2$ Hz, 1H; ArH), 6.89 (t, $J = 8.2$ Hz, 1H; ArH), 5.95 (t, $J = 7.2$ Hz, 1H; CH), 4.04 (d, $J = 7.2$ Hz, 2H; CH_2), 1.94 (s, $^3J(Sn,H) = 64.4$ Hz, 3H; CH_3), 1.80–1.60 (m, 6H; CH_2), 1.60–1.50 (m, 6H; CH_2), 1.10–1.00 ppm (m, 15H; $CH_2 + CH_3$); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 166.7$ (s), 154.0 (s), 145.4 (s), 135.9 (s), 133.8 (d), 126.1 (d), 124.3 (d), 121.8 (d), 121.1 (d), 30.7 (t), 29.6 (t, $^3J(Sn,C) = 19.7$ Hz), 27.7 (t, $^2J(Sn,C) = 54.1$ Hz), 19.3 (q), 13.9 (q), 9.5 ppm (t, $^1J(Sn,C) = 330.5$ Hz); IR (NaCl): $\tilde{\nu} = 2954$ (s, C–H), 2923 (s, C–H), 2850 (m, C–H), 1458 (m), 1427 (m), 994 cm^{-1} (m); MS (FAB^+): *m/z* (%): 513 $[M+3]^+$ (10), 512 $[M+2]^+$ (35), 511 $[M+1]^+$ (16), 510 $[M]^+$ (28), 509 (12), 508 (15), 458 (18), 456 (26), 455 (25), 454 (100), 453 (41), 452 $[M-Bu]^+$ (74), 451 (29), 450 (39), 400 (23), 399 (10), 398 (18), 396 (12), 291 (21), 289 (20), 287 (13), 286 (31), 285 (11), 284 (23), 282 (13), 235 (20), 233 (18), 231 (12), 220 (16), 188 (15); HRMS (FAB^+): *m/z*: calcd for $C_{23}H_{38}NS_2{}^{118}Sn$: 510.1462; found: 510.1450.

(*E*)-1-(Benzothiazol-2-yl)sulfonyl-3-(tri-*n*-butyltin)-3-methylprop-2-ene (11). General procedure for sulfone formation: A solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (1.21 g, 0.98 mmol) in 35% aqueous hydrogen peroxide (6.32 mL, 73.54 mmol) was added to a solution of **26** (2.5 g, 4.90 mmol) in EtOH (250 mL). After stirring for 2.5 h, a 20% aqueous $Na_2S_2O_5$ solution (150 mL) was added and the resulting mixture was extracted with Et_2O (3×). The combined organic layers were washed with brine (2×), dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (silica gel, 85:12:3 hexane/EtOAc/Et_3N) and crystallization to afford 2.97 g (56%) of a white solid identified as **11**. M.p. 78–79 °C (Et_2O/hexane); ^1H NMR (400 MHz, C_6D_6): $\delta = 7.93$ (d, $J = 8.2$ Hz, 1H; ArH), 7.12 (d, $J = 8.5$ Hz, 1H; ArH), 7.04 (t, $J = 8.1$ Hz, 1H; ArH), 6.91 (t, $J = 8.0$ Hz, 1H; ArH), 5.70 (tq, $J = 7.4$, 1.8, $^3J(Sn,H) = 63.0$ Hz, 1H; CH), 4.12 (dd, $J = 7.4$, 3.8 Hz, 2H; CH_2), 1.69 (d, $J = 1.5$, $^3J(Sn,H) = 62.4$ Hz, 3H; CH_3), 1.40–1.30 (m, 6H; CH_2), 1.30–1.20 (m, 6H; CH_2), 0.90–0.80 ppm (m, 15H; $CH_2 + CH_3$); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 167.6$ (s), 153.2 (s), 153.1 (s), 137.1 (s), 128.3 (d), 127.4 (d), 125.1 (d), 123.6 (d, $^2J(Sn,Csp^2) = 19.5$ Hz), 122.3 (d), 53.4 (t, $^3J(Sn,C) = 57.8$ Hz), 29.3 (t, $^3J(Sn,C) = 20.3$ Hz), 27.6 (t, $^2J(Sn,C) = 57.5$ Hz), 19.7 (q), 13.8 (q), 9.5 ppm (t, $^1J(Sn,C) = 325.7$ Hz); IR (NaCl): $\tilde{\nu} = 2956$ (s, C–H), 2926 (s, C–H), 1472 (m), 1318 (s), 1139 cm^{-1} (m); UV (MeOH): $\lambda_{max} = 238$, 274 nm; MS (FAB^+): *m/z* (%): 544 $[M+1]^+$ (7), 486 (21), 422 (25), 420 (20), 416 (17), 368 (28), 366 (22), 302 (27), 300 (20), 291 (23), 289 (20), 287 (17), 256 (22), 254 (53), 253 (20), 252 (38), 250 (18), 235 (37), 233 (32), 231 (24), 200 (18), 181 (17), 179 (77), 178 (22), 177 (100), 176 (32), 175 (79), 174 (18), 173 (37), 159 (17), 157 (16), 155 (15), 154 (17); HRMS (FAB^+): *m/z*: calcd for $C_{23}H_{38}NO_2S_2{}^{120}Sn$: 544.1366; found: 544.1350; elemental analysis calcd for $C_{23}H_{37}NO_2S_2Sn$: C 50.93, H 6.88; found: C 51.05, H 6.93.

(−)-(1*R*,2a*S*,3′*E*)-2-[5-(Benzothiazol-2-sulfonyl)-3-methylpenta-1,3-dienyliden]-1,3,3-trimethylcyclohexanol ((a*S*)-10a). General procedure for the Stille reaction of bromoallenes: $[PdCl_2(PhCN)_2]$ (0.006 g, 0.016 mmol) was added to a solution of **12a** (0.020 g, 0.082 mmol) in DMF (1 mL). After stirring for 5 min at 25 °C, a solution of **11** (0.066 g, 0.122 mmol) in THF (0.8 mL) was added and the mixture was deoxygenated with freeze–thaw cycles (3×). A solution of iPr_2NEt (0.021 mL, 0.123 mmol) was added and the resulting mixture was stirred for 1.5 h at 40 °C. A saturated aqueous KF solution was added and the layers were separated. The aqueous layer was extracted with EtOAc (3×). The com-

bined organic layers were washed with brine (3×), dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (silica gel, 70:30 hexane/EtOAc) to afford 24 mg (69%) of an orange oil (foam) identified as (a*S*)-**10a**. $[\alpha]_D^{20}=-21.84$ ($c=0.02$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.18$ (d, $J=8.1$ Hz, 1H; ArH), 7.95 (d, $J=7.8$ Hz, 1H; ArH), 7.60–7.50 (m, 2H; ArH), 5.93 (s, 1H; CH), 5.38 (t, $J=8.1$ Hz, 1H; CH), 4.30 (dd, $J=8.1$, 4.1 Hz, 2H; CH_2), 1.90–1.80 (m, 1H; CH_2), 1.70–1.60 (m, 1H; CH_2), 1.47 (s, 3H; CH_3), 1.50–1.40 (m, 2H; CH_2), 1.30–1.20 (m, 2H; CH_2), 1.14 (s, 3H; CH_3), 1.06 (s, 3H; CH_3), 0.85 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.4$ (s), 165.5 (s), 152.5 (s), 141.8 (s), 127.8 (d), 127.5 (d), 125.3 (d), 122.1 (d), 120.1 (s), 110.4 (d), 101.3 (d), 70.7 (s), 55.3 (t), 40.0 (t), 39.9 (t), 34.2 (s), 31.2 (q), 30.9 (q), 29.1 (q), 18.1 (t), 14.0 ppm (q); IR (NaCl): $\tilde{\nu}=3600$–3400 (br, OH), 3000–2800 (s, C–H), 1937 (w, C=C=C), 1471 (s), 1328 (s), 1149 cm^{-1} (s); MS (EI$^+$): *m*/*z* (%): 328 (30), 268 (29), 165 (89), 161 (22), 151 (100), 145 (33), 135 (24), 134 (40), 132 (29), 122 (20), 121 (21), 107 (22), 93 (20), 77 (25), 69 (66), 67 (24), 65 (72); HRMS (EI$^+$): *m*/*z*: calcd for $C_{22}H_{27}NO_3S_2$: 417.1432; found: 417.1417.

(−)-(1*S*,3*R*,4a*S*,3′*E*)-4-[5-(Benzothiazol-2-sulfonyl)-3-methylpenta-1,3-dienyliden]-3-hydroxy-3,5,5-trimethylcyclohexyl acetate ((a*S*)-10d): Following the general procedure for the Stille reaction of bromoallenes, the reaction of **12d** (0.050 g, 0.165 mmol) with **11** (0.134 g, 0.248 mmol), [$PdCl_2$(PhCN)$_2$] (0.013 g, 0.033 mmol) and (iPr)$_2$NEt (0.043 mL, 0.248 mmol) in DMF (2.0 mL) and THF (1.6 mL) afforded, after purification by column chromatography (silica gel, 70:30→60:40 hexane/EtOAc), 0.05 g (64%) of an orange solid identified as (a*S*)-**10d**. $[\alpha]_D^{24}=-30.4$ ($c=0.05$ in $CHCl_3$); m.p. 133–134 °C (hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.18$ (d, $J=7.7$ Hz, 1H; ArH), 7.95 (d, $J=7.5$ Hz, 1H; ArH), 7.60–7.50 (m, 2H; ArH), 6.00 (s, 1H; CH), 5.42 (t, $J=8.1$ Hz, 1H; CH), 5.26 (m, 1H; CH), 4.31 (d, $J=8.1$ Hz, 2H; CH_2), 2.14 (ddd, $J=12.8$, 4.1, 2.1 Hz, 1H; CH_2), 1.98 (s, 3H; CH_3), 1.85 (ddd, $J=12.3$, 4.0, 2.0 Hz, 1H; CH_2), 1.50 (s, 3H; CH_3), 1.50–1.20 (m, 2H; CH_2), 1.21 (s, 3H; CH_3), 1.16 (s, 3H; CH_3), 0.88 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 201.7 (s), 170.3 (s), 165.5 (s), 152.5 (s), 141.3 (s), 137.0 (s), 127.9 (d), 127.6 (d), 125.3 (d), 122.2 (d), 117.7 (s), 111.1 (d), 101.7 (d), 72.2 (s), 67.7 (d), 55.2 (t), 44.8 (t, 2×), 35.2 (s), 31.8 (q), 30.9 (q), 29.2 (q), 21.2 (q), 14.1 ppm (q); IR (NaCl): $\tilde{\nu}=3600$–3100 (br, OH), 2962 (s, C–H), 2924 (s, C–H), 2852 (w, CH), 1939 (w, C=C=C), 1726 (s, C=O), 1250 (s, C–O), 1186 cm^{-1} (s); MS (EI$^+$): *m*/*z* (%): 475 [*M*]$^+$ (8), 411 (22), 385 (20), 382 (43), 277 (89), 276 (36), 268 (27), 217 (99), 216 (24), 214 (27), 201 (41), 200 (30), 199 (29), 189 (68), 187 (22), 173 (41), 163 (41), 161 (30), 159 (100), 158 (22), 157 (21), 145 (22), 143 (26), 136 (68), 135 (77), 133 (67), 131 (27), 121 (24), 119 (35), 117 (21), 108 (25), 107 (22), 105 (43), 95 (23), 91 (36); HRMS (EI$^+$): *m*/*z*: calcd for $C_{24}H_{29}NO_5S_2$: 475.1487; found: 475.1487; elemental analysis calcd for $C_{24}H_{29}NO_5S_2$: C 60.61, H 6.15, N 2.94, S 13.48; found: C 60.44, H 6.15, N 2.92, S 13.25.

(−)-(1*R*,2a*S*,3′*E*,5′*Z*,7′*E*)-2-(3-Methyl-8-tributyltin-octa-1,3,5,7-tetraenyliden)-1,3,3-trimethylcyclohexan-1-ol ((a*S*)-8a). General procedure for the modified Julia olefination: A cooled (−78 °C) solution of (a*S*)-**10a** (0.051 g, 0.12 mmol) in THF (6 mL) was treated with NaHMDS (0.37 mL, 1 M in THF, 0.37 mmol). After stirring for 30 min at this temperature, a solution of 3-tri-*n*-butyltinpropen-1-al **9** (0.063 g, 0.18 mmol) in THF (3 mL) was added and the resulting mixture was stirred for 2 h at −78 °C. Water was added at low temperature and the mixture was warmed up to room temperature. It was then diluted with Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3×), the combined organic layers were dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography (silica gel, 93:5:2 hexane/EtOAc/Et_3N) to afford 52.5 mg (79%) of a yellow oil identified as a mixture of 5′*Z*/5′*E* isomers of (a*S*)-**8a** in a 5:1 ratio.

*Data for (1*R*,2a*S*,3′*E*,5′*Z*,7′*E*)-**8a***: $[\alpha]_D^{22}=-26.1$ ($c=0.05$ in $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): $\delta=7.44$ (dd, $J=18.5$, 10.6, ^3J(Sn,H)=59.1 Hz, 1H; CH), 6.76 (d, $J=11.7$ Hz, 1H; CH), 6.53 (d, $J=18.5$, ^2J(Sn,H)= 71.2 Hz, 1H; CH), 6.29 (t, $J=11.0$ Hz, 1H; CH), 6.19 (t, $J=10.7$ Hz, 1H; CH), 6.04 (s, 1H; CH), 1.89 (m, 1H; CH_2), 1.76 (s, 3H; CH_3), 1.72 (m, 1H; CH_2), 1.70–1.50 (m, 7H; CH_2), 1.50–1.30 (m, 12H; CH_2+CH_3), 1.24 (s, 3H; CH_3), 1.07 (s, 3H; CH_3), 1.01 (m, 6H; CH_2), 0.92 ppm (m, 9H; CH_3); ^{13}C NMR (100 MHz, C_6D_6): $\delta=202.7$ (s), 143.2 (d), 136.3 (d), 134.6 (s), 132.2 (d), 125.3 (d), 123.6 (d), 120.4 (s), 104.0 (d), 71.2 (s), 41.0 (t, 2×), 35.1 (s), 32.4 (q), 31.9 (q), 30.1 (t, ^3J(Sn,H)=20.9 Hz, 3×), 29.9 (q), 28.1 (t, ^2J(Sn,H)=55.4 Hz, 3×), 19.1 (t), 14.5 (q), 14.3 (q), 10.3 ppm (t, ^1J(Sn,H)=336.5 Hz; 3×); IR (NaCl): $\tilde{\nu}=3500$–3300 (br, OH), 2957 (s, C–H), 2925 (s, C–H), 2870 (s, C–H), 1927 (w, C=C=C), 1686 (w), 1600 (w), 1460 cm^{-1} (m); UV (MeOH): $\lambda_{max}=308$, 320, 334 nm; MS (FAB$^+$): *m*/*z* (%): 491 [*M*−Bu]$^+$ (35), 489 (29), 475 (20), 474 (29), 473 (90), 472 (42), 471 (70), 470 (32), 469 (39), 359 (24), 357 (22), 291 (71), 290 (31), 289 (63), 288 (27), 287 (38), 251 (20), 239 (43), 235 (52), 234 (23), 233 (42), 231 (29), 183 (21), 179 (98), 178 (31), 177 (100), 176 (35), 175 (66), 169 (20), 165 (28); HRMS (FAB$^+$): *m*/*z*: calcd for $C_{30}H_{53}O^{120}Sn$: 549.3118; found: 549.3111.

(−)-(1*S*,3*R*,4a*S*,3′*E*,5′*Z*,7′*E*)-3-Methyl-4-[8-(tributyltin)octa-1,3,5,7-tetraenyliden]-3-hydroxy-3,5,5-trimethylcyclohexyl acetate ((a*S*)-8d): Following the general procedure for the modified Julia olefination, the reaction of (a*S*)-**10d** (0.23 g, 0.47 mmol) with NaHMDS (1.42 mL, 1 M in THF, 1.42 mmol) and (*E*)-3-tri-*n*-butyltinpropen-1-al **9** (0.24 g, 0.71 mmol) in THF (33 mL) afforded, after purification by column chromatography (silica gel, 90:8:2 hexane/EtOAc/Et_3N), 149 mg (70%) of a yellow oil identified as (a*S*)-**8d**. $[\alpha]_D^{22}=-59.9$ ($c=0.04$ in $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): $\delta=7.43$ (dd, $J=18.5$, 10.4 Hz, 1H; CH), 6.75 (d, $J=$ 11.6 Hz, 1H; CH), 6.55 (d, $J=18.5$ Hz, 1H; CH), 6.25 (t, $J=11.0$ Hz, 1H; CH), 6.20 (t, $J=10.5$ Hz, 1H; CH), 6.03 (s, 1H; CH), 5.66 (ddd, $J=$ 11.5, 7.3, 4.2 Hz, 1H; CH), 2.23 (ddd, $J=12.6$, 4.1, 2.1 Hz, 1H; CH_2), 2.00 (ddd, $J=12.2$, 4.0, 2.0 Hz, 1H; CH_2), 1.72 (s, 3H; CH_3), 1.71 (s, 3H; CH_3), 1.60–1.50 (m, 6H; CH_2), 1.44 (s, 3H; CH_3), 1.40–1.30 (m, 8H; CH_2), 1.15 (s, 3H; CH_3), 1.10–1.00 (m, 6H; CH_2), 1.03 (s, 3H; CH_3), 1.00–0.90 ppm (m, 9H; CH_3); ^{13}C NMR (100 MHz, C_6D_6): $\delta=202.2$ (s), 169.3 (s), 142.3 (d), 136.0 (d), 133.4 (s), 131.7 (d), 124.4 (d), 123.3 (d), 117.4 (s), 103.5 (d), 72.1 (s), 67.7(d), 45.2 (t, 2×), 35.3 (s), 32.0 (q), 30.8 (q), 29.2 (q), 29.2 (t), 27.3 (t), 20.6 (q), 13.7 (q), 13.6 (q), 9.6 ppm (t); IR (NaCl): $\tilde{\nu}=3359$ (m), 3194 (m), 2959 (s, C–H), 2924 (s, C–H), 2852 (s, C–H), 1932 (w, C=C=C), 1721 (m, C=O), 1660 (s), 1632 (s), 1466 (m), 1262 cm^{-1} (s, C–O); UV (MeOH): $\lambda_{max}=306$, 319, 332 nm; MS (FAB$^+$): *m*/*z* (%): 549 [*M*]$^+$ (4), 547 (3), 545 (2), 531 (13), 530 (6), 529 (12), 473 (10), 471 (20), 469 (13), 297 (13), 295 (19), 293 (81), 292 (31), 291 (96), 290 (35), 289 (70), 288 (18), 287 (25), 239 (18), 237 (24), 235 (41), 234 (14), 233 (32), 232 (12), 231 (20), 183 (19), 181 (21), 179 (100), 178 (30), 177 (99), 176 (33), 175 (66), 174 (10), 173 (18); HRMS (FAB$^+$): *m*/*z*: calcd for $C_{28}H_{45}O_3{}^{116}Sn$: 545.2386; found: 545.2388; calcd for $C_{28}H_{45}O_3{}^{120}Sn$: 549.2391; found: 549.2385.

(*Z*)-3-Bromo-5-((2*E*,4*E*,6*E*,8*E*)-11-((*R*)-2-hydroxy-2,6,6-trimethylcyclohexylidene)-2,9-dimethylundeca-2,4,6,8,10-pentaenylidene)furan-2(5*H*)-one ((a*S*,11′*Z*)-29a). General procedure for Stille cross-coupling: [$AsPh_3$] (0.005 g, 0.017 mmol) was added to a solution of [Pd_2(dba)$_3$]·$CHCl_3$ (0.002 g, 0.002 mmol) in THF (0.7 mL). After stirring for 5 min, **6** (0.023 g, 0.068 mmol) was added and the mixture was stirred for 10 min. A solution of (a*S*,5′*Z*)-**8a** (0.045 g, 0.081 mmol) in THF (0.7 mL) and $Bu_4NPh_2PO_2$ (0.031 g, 0.068 mmol) in one portion were sequentially added. After stirring for 4.5 h at 25 °C, brine was added and the mixture was extracted with EtOAc/CH_2Cl_2 90:10 (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 90:10→80:20 hexane/EtOAc) to afford 27.9 mg (87%) of a red solid identified as a mixture of (a*S*,11′*Z*)-**29a** and its isomer (a*S*,11′*E*)-**29a** in a 1:3.5 ratio.

*Data for (a*S*,11′Z)-**29a***: ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.41$ (s, 1H; CH), 6.95 (t, $J=12.5$ Hz, 1H; CH), 6.58 (dd, $J=12.7$, 11.9 Hz, 1H; CH), 6.55 (d, $J=11.9$ Hz, 1H; CH), 6.50 (d, $J=12.2$ Hz, 1H; CH), 6.40 (t, $J=$ 11.5 Hz, 1H; CH), 6.12 (t, $J=11.3$ Hz, 1H; CH), 6.12 (s, 1H; CH), 5.76 (s, 1H; CH), 2.20 (s, 3H; CH_3), 1.90 (m, 1H; CH_2), 1.83 (s, 3H; CH_3), 1.80 (m, 1H; CH_2), 1.55–1.45 (m, 3H; CH_2), 1.40–1.30 (m, 1H; CH_2), 1.31 (s, 3H; CH_3), 1.26 (s, 3H; CH_3), 1.02 ppm (s, 3H; CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=202.4$ (s), 165.7 (s), 146.1 (s), 142.2 (d), 139.6 (d), 135.8 (s), 133.4 (s), 132.9 (d), 129.4 (d), 128.5 (d), 128.3 (d), 122.8 (d), 120.4 (s), 120.2 (d), 109.1 (s), 103.6 (d), 71.1 (s), 40.2 (t, 2×), 34.6 (s), 31.9 (q), 31.8 (q), 29.5 (q), 18.4 (t), 15.4 (q), 14.1 ppm (q); IR (NaCl): $\tilde{\nu}=$ 3700–3600 (br, OH), 2922 (w, C–H), 1755 (s, C=O), 1519 (m), 1346 (w), 1184 (w), 977 cm^{-1} (m); MS (FAB$^+$): *m*/*z* (%): 473 [*M*+1]$^+$, 36), 472

$[M]^+$, 100), 471 $[M+1]^+$ (36), 470 $[M]^+$ (100), 393 (79), 282 (71); HRMS (FAB^+): *m/z*: calcd for $C_{26}H_{31}{}^{79}BrO_3$: 470.1457; found: 470.1473; calcd for $C_{26}H_{31}{}^{81}BrO_3$: 472.1436; found: 472.1436.

*Data for (a**S**,11′**E**)-**29a***: ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.40$ (s, 1H; CH), 6.64 (dd, $J=14.5$, 11.8 Hz, 1H; CH), 6.60–6.50 (m, 2H; CH), 6.48 (d, $J=10.7$ Hz, 1H; CH), 6.33 (dd, $J=14.5$, 10.1 Hz, 1H; CH), 6.08 (d, $J=11.1$ Hz, 1H; CH), 6.08 (s, 1H; CH), 5.77 (s, 1H; CH), 2.19 (s, 3H; CH_3), 1.89 (m, 1H; CH_2), 1.83 (s, 3H; CH_3), 1.77 (m, 1H; CH_2), 1.55–1.45 (m, 3H; CH_2), 1.34 (m, 1H; CH_2), 1.30 (s, 3H; CH_3), 1.25 (s, 3H; CH_3), 1.01 ppm (s, 3H; CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=202.3$ (s), 165.8 (s), 145.9 (s), 142.2 (d), 139.8 (d), 138.4 (d), 135.5 (s), 133.0 (s), 132.4 (d, 2×), 128.4 (d), 127.9 (d), 120.4 (d), 120.4 (s), 108.9 (s), 103.5 (d), 71.1 (s), 40.2 (t, 2×), 34.6 (s), 31.4 (q), 31.2 (q), 29.6 (q), 18.4 (t), 15.2 (q), 14.3 ppm (q); IR (NaCl): $\tilde{\nu}=2958$ (s, C–H), 2924 (s, C–H), 2851 (m, C–H), 1756 (s, C=O), 1518 (w), 1345 (w), 979 cm^{-1} (s); UV (MeOH): $\lambda_{max}=289$, 458 nm; MS (FAB^+): *m/z* (%): 473 $[M+1]^+$ (5), 472 $[M]^+$ (11), 470 $[M]^+$ (10), 307 (17), 289 (15), 202 (17), 189 (16), 180 (21), 178 (21), 167 (19), 165 (34); HRMS (FAB^+): *m/z*: calcd for $C_{26}H_{31}{}^{79}BrO_3$: 470.1457; found: 470.1464; calcd for $C_{26}H_{31}{}^{81}BrO_3$: 472.1436; found: 472.1458.

(1*S*,3*R*)-4-[(3*E*,5*E*,7*E*,9*E*,11*Z*)-11-(4-Bromo-5-oxofuran-2(5*H*)-ylidene)-3,10-dimethylundeca-1,3,5,7,9-pentaenylidene]-3-hydroxy-3,5,5-trimethylcyclohexyl acetate ((a*S*,11′*Z*)-29d): Following the general procedure for the Stille cross-coupling, the reaction of (a*S*,5′*Z*)-**8a** (0.169 g, 0.279 mmol) with **6** (0.127 g, 0.372 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.005 g, 0.005 mmol), $[AsPh_3]$ (0.013 g, 0.042 mmol), $Bu_4NPh_2PO_2$ (0.107 g, 0.232 mmol) and BHT (traces) in THF (5 mL) for 5.5 h at 25 °C, afforded, after purification by column chromatography (silica gel, 80:20→70:30 hexane/EtOAc), 84 mg (68 %) of a red solid identified as a mixture of (a*S*,11′*Z*)-**29d** and its isomer (a*S*,11′*E*)-**29d** in a 1:5 ratio.

*Data for (a**S**,11′**Z**)-**29d***: ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.43$ (s, 1H; CH), 6.95 (t, $J=12.3$ Hz, 1H; CH), 6.59 (t, $J=12.6$ Hz, 1H; CH), 6.55 (d, $J=12.3$ Hz, 1H; CH), 6.52 (d, $J=12.3$ Hz, 1H; CH), 6.41 (t, $J=11.7$ Hz, 1H; CH), 6.18 (s, 1H; CH), 6.14 (t, $J=11.5$ Hz, 1H; CH), 5.77 (s, 1H; CH), 5.35 (m, 1H; CH), 2.30–2.20 (m, 1H; CH_2), 2.20 (s, 3H; CH_3), 2.01 (s, 3H; CH_3), 1.94 (d, $J=10.6$ Hz, 1H; CH_2), 1.83 (s, 3H; CH_3), 1.50–1.40 (m, 1H; CH_2), 1.40 (s, 3H; CH_3), 1.40–1.30 (m, 1H; CH_2), 1.33 (s, 3H; CH_3), 1.05 ppm (s, 3H; CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=202.8$ (s), 170.4 (s), 165.7 (s), 146.1 (s), 142.2 (d), 139.5 (d), 135.1 (s), 133.4 (s), 132.8 (d), 129.5 (d), 128.8 (d), 128.0 (d), 123.2 (d), 120.2 (d), 117.7 (s), 109.1 (s), 103.8 (d), 72.6 (s), 67.9 (d), 45.0 (t), 44.9 (t), 35.5 (s), 32.0 (q), 31.2 (q), 29.4 (q), 21.3 (q), 15.3 (q), 14.1 ppm (q); IR (NaCl): $\tilde{\nu}=3600$–3100 (br, OH), 2961 (w, C–H), 2924 (w, C–H), 2853 (w, C–H), 1929 (w, C=C=C), 1755 (s, C=O), 1554 (m), 1260 (m), 976 cm^{-1} (m); UV (MeOH): $\lambda_{max}=244$, 289, 456 nm; MS (FAB^+): *m/z* (%): 531 (13), 530 $[M]^+$, 55), 529 (13), 528 $[M]^+$ (47), 453 (32), 451 (29); HRMS (EI^+): *m/z*: calcd for $C_{28}H_{33}{}^{79}BrO_5$: 528.1511; found: 528.1530; calcd for $C_{28}H_{33}{}^{81}BrO_5$: 530.1491; found: 530.1481.

3,3′-Didehydroxy-6′-*epi*-peridinin (30): Following the general procedure for the Stille cross-coupling, the reaction of bromide (a*S*,11′*Z*)-**29a** (0.021 g, 0.045 mmol) with **7b** (0.025 g, 0.054 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.001 g, 0.001 mmol), $[AsPh_3]$ (0.002 g, 0.007 mmol) and $Bu_4NPh_2PO_2$ (0.021 g, 0.045 mmol) in THF (2.0 mL) at 55 °C for 20 h afforded, after purification by column chromatography (silica gel, 80:20→70:30 hexane/EtOAc), 3.5 mg (21 % yield based on recovered starting material) of a red solid identified as 6′-*epi*-**30** and 7.0 mg of starting (a*S*,11′*Z*)-**29a**. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.13$ (d, $J=15.8$ Hz, 1H; CH), 6.98 (s, 1H; CH), 6.60–6.40 (m, 3H; CH), 6.41 (d, $J=10.9$ Hz, 1H; CH), 6.30–6.20 (m, 1H; CH), 6.34 (d, $J=15.7$ Hz, 1H; CH), 6.08 (d, $J=12.1$ Hz, 1H; CH), 6.08 (s, 1H; CH), 5.69 (s, 1H; CH), 2.34 (t, $J=8.1$ Hz, 1H; CH_2), 2.20 (s, 3H; CH_3), 1.99 (m, 1H; CH_2), 1.90–1.70 (m, 6H; CH_2), 1.83 (s, 3H; CH_3), 1.52 (s, 3H; CH_3), 1.50–1.30 (m, 3H; CH_2), 1.30 (s, 3H; CH_3), 1.30–1.20 (m, 1H; CH_2), 1.25 (s, 3H; CH_3), 1.13 (s, 6H; CH_3), 1.01 ppm (s, 3H; CH_3); IR (NaCl): $\tilde{\nu}=3000$–2850 (s, CH), 1930 (w, C=C=C), 1751 cm^{-1} (s, C=O); MS (FAB^+): *m/z* (%): 557 $[M+1]^+$ (18), 556 $[M]^+$ (30), 539 (12), 307 (37), 289 (17); HRMS (FAB^+): *m/z*: calcd for $C_{37}H_{49}O_4$: 557.3631; found: 557.3616.

6′-*epi*-Peridinin 6′-*epi*-(1): Following the general procedure for the Stille cross-coupling, the reaction of (a*S*,11′*Z*)-**29d** (0.019 g, 0.035 mmol) with **7b** (0.02 g, 0.043 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.002 g, 0.002 mmol), $[AsPh_3]$ (0.0043 g, 0.014 mmol), $Bu_4NPh_2PO_2$ (0.016 g, 0.035 mmol) and BHT (traces) in THF (1.5 mL) for 31 h at 55 °C, afforded, after purification by column chromatography (silica gel, 70:30→0:100 hexane/EtOAc), 15.9 mg (72 %) of a red solid identified as 6′-*epi*-**1**. ^{1}H NMR (750 MHz, $(CD_3)_2CO$): $\delta=7.57$ (s, 1H; CH), 7.22 (d, $J=15.2$ Hz, 1H; CH), 6.82 (dd, $J=14.2$, 11.2 Hz, 1H; CH), 6.80 (dd, $J=14.0$, 11.2 Hz, 1H; CH), 6.68 (dd, $J=14.0$, 11.8 Hz, 1H; CH), 6.62 (d, $J=11.2$ Hz, 1H; CH), 6.52 (dd, $J=14.2$, 11.2 Hz, 1H; CH), 6.42 (d, $J=15.4$ Hz, 1H; CH), 6.26 (s, 1H; CH), 6.23 (d, $J=11.0$ Hz, 1H; CH), 6.09 (s, 1H; CH), 5.40 (m, 1H; CH), 4.23 (s, 1H; OH), 3.86 (s, 1H; OH), 3.77 (m, 1H; CH), 2.30 (dd, $J=14.4$, 3.2 Hz, 1H; CH_2), 2.17 (d, $J=12.0$ Hz, 1H; CH_2), 2.01 (s, 3H; CH_3), 1.93 (m, 1H; CH_2), 1.91 (s, 3H; CH_3), 1.68 (dd, $J=14.3$, 9.3 Hz, 1H; $2H_2$), 1.57 (d, $J=12.7$ Hz, 1H; CH_2), 1.46 (s, 3H; CH_3), 1.44 (d, $J=12.1$ Hz, 1H; CH_2), 1.40–1.30 (m, 1H; CH_2), 1.35 (s, 3H; CH_3), 1.29 (t, $J=12.0$ Hz, 1H; CH_2), 1.19 (s, 3H; CH_3), 1.17 (s, 3H; CH_3), 1.06 (s, 3H; CH_3), 0.94 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta=204.4$ (s), 171.4 (s), 170.2 (s), 149.0 (s), 140.0 (d), 139.5 (d), 138.8 (d), 137.0 (s), 135.6 (d), 135.3 (s), 134.7 (d), 133.7 (d), 130.7 (d), 130.0 (d), 126.4 (s), 123.6 (d), 120.7 (d), 119.5 (s), 104.9 (d), 73.4 (s), 71.8 (s), 69.5 (d), 69.0 (s), 64.7 (d), 48.9 (t), 47.5 (t), 47.2 (t), 42.8 (t), 37.2 (s), 36.8 (s), 33.7 (q), 32.2 (q), 31–30 (q, 2×), 26.4 (q), 22.2 (q), 21.2 (q), 16.4 (q), 15.5 ppm (q); IR (NaCl): $\tilde{\nu}=3500$–3300 (br, OH), 3359 (s), 3000–2850 (s, C–H), 1926 (w, C=C=C), 1750 cm^{-1} (s, C=O); MS (FAB^+): *m/z* (%): 631 $[M+1]^+$ (6), 630 $[M]^+$ (12), 252 (20), 241 (22), 239 (34), 228 (23), 227 (22), 226 (22), 215 (21), 204 (23), 202 (30). 191 (26), 190 (23), 189 (30), 181 (24), 180 (32), 179 (23), 178 (41), 176 (28), 168 (20), 167 (40), 166 (30), 165 (74); HRMS (FAB^+): *m/z*: calcd for $C_{39}H_{50}O_7$: 630.3557; found: 630.3550; calcd for $C_{39}H_{51}O_7$: 631.3635; found: 631.3637.

(5*Z*,2′*E*,4′*E*)-3-Bromo-5-(6-hydroxy-2-methylhexa-2,4-dienyliden)-5*H*-furan-2-one (15): Following the general procedure for the Stille cross-coupling, the reaction of **6** (0.053 g, 0.154 mmol) with **31** (0.067 g, 0.193 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.003 g, 0.003 mmol), $[AsPh_3]$ (0.008 g, 0.025 mmol) and $Bu_4NPh_2PO_2$ (0.071 g, 0.145 mmol) in THF (3.4 mL) for 4.5 h afforded, after purification by column chromatography (silica gel, 60:40→50:50 hexane/EtOAc), 28.2 mg (68 %) of a red solid identified as **15**. M.p. 111–113 °C (CH_2Cl_2/Et_2O); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=7.42$ (s, 1H; CH), 6.63 (ddt, $J=15.0$, 11.3, 1.6 Hz, 1H; CH), 6.42 (d, $J=11.3$ Hz, 1H; CH), 6.05 (dt, $J=15.1$, 5.5 Hz, 1H; CH), 5.73 (s, 1H; CH), 4.26 (d, $J=5.4$ Hz, 2H; CH_2), 2.22 ppm (s, 3H; CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=165.7$ (s), 146.2 (s), 142.5 (d), 138.0 (d), 137.2 (d), 133.1 (s), 126.7 (d), 119.9 (d), 109.9 (s), 63.3 (t), 15.2 ppm (q); IR (NaCl): $\tilde{\nu}=3600$–3200 (br, OH), 2924 (w, C–H), 2852 (w, C–H), 1755 (s, C=O), 1606 (w), 1344 (w), 985 cm^{-1} (s); UV (MeOH): $\lambda_{max}=248$, 348, 368, 387 nm; MS (EI^+): *m/z* (%): 272 $[M]^+$ (14), 270 $[M]^+$ (21), 188 (70), 187 (23), 145 (23), 135 (30), 133 (30), 120 (30), 119 (100), 116 (20), 115 (36), 107 (49), 95 (28), 92 (41), 91 (58), 79 (55), 78 (20), 77 (46), 67 (23), 65 (23); HRMS (EI^+): *m/z*: calcd for $C_{11}H_{11}{}^{79}BrO_3$: 269.9892; found: 269.9892; calcd for $C_{11}H_{11}{}^{81}BrO_3$: 271.9871; found: 271.9867.

(−)-3-Dehydroxy-14′-apo-peridinin-14′-ol (32): Following the general procedure for the Stille cross-coupling, the reaction of **15** (0.028 g, 0.104 mmol) with **7a** (0.057 g, 0.125 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.002 g, 0.002 mmol), $[AsPh_3]$ (0.0043 g, 0.014 mmol) and $Bu_4NPh_2PO_2$ (0.048 g, 0.104 mmol) in THF (4.0 mL) at 55 °C for 20 h afforded, after purification by column chromatography (silica gel, 60:40→50:50 hexane/EtOAc), 16.6 mg (45 %) of a yellow oil identified as **32**; $[\alpha]_D^{23}=-83.8$ ($c=0.05$ in $CHCl_3$); ^{1}H NMR (600 MHz, $(CD_3)_2CO$): $\delta=7.49$ (s, 1H; CH), 7.16 (d, $J=15.5$ Hz, 1H; CH), 6.73 (ddt, $J=15.0$, 11.3, 1.8 Hz, 1H; CH), 6.51 (d, $J=11.3$ Hz, 1H; CH), 6.39 (d, $J=15.5$ Hz, 1H; CH), 6.08 (dt, $J=15.0$, 5.2 Hz, 1H; CH), 5.95 (s, 1H; CH), 4.22 (brs, 2H; CH_2), 3.89 (s, 1H; OH), 2.18 (s, 3H; CH_3), 1.90–1.80 (m, 2H; CH_2), 1.50–1.40 (m, 3H; CH_2), 1.16 (s, 3H; CH_3), 1.13 (s, 3H; CH_3), 1.11 (m, 1H; CH_2), 0.91 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta=169.3$ (s), 147.9 (s), 139.6 (d), 138.1 (d), 138.0 (d), 134.5 (d), 133.3 (s), 126.3 (d), 125.8 (s), 122.6 (d), 119.5 (d), 71.7 (s), 66.4 (s), 63.0 (t), 36.6 (t), 34.4 (s), 30.8 (t), 26.4 (q), 26.2 (q), 21.1 (q), 17.8 (t), 15.4 ppm (q); IR (NaCl): $\tilde{\nu}=3600$–3200 (br, OH), 2961 (s, C–H), 2926 (s, C–H), 2860 (m), 1751 (s, C=O),

1261 (s), 1091 (s), 1024 cm^{-1} (s); UV (MeOH): $\lambda_{max}=247$, 377 nm; MS (EI^+): m/z (%): 357 $[M+1]^+$ (6), 356 $[M]^+$ (24), 355 (20), 346 (20), 344 (22), 338 (29), 281 (16), 253 (21), 232 (46), 109 (15), 91 (18), 83 (16), 81 (22), 73 (20), 71 (15), 69 (100); HRMS (EI^+): m/z: calcd for $C_{22}H_{28}O_4$: 356.1988; found: 356.1981.

(−)-3-Dehydroxy-14′-apo-peridinin-14′-al (33): A solution of **32** (0.017 g, 0.048 mmol) in CH_2Cl_2 (0.3 mL) was added to a cooled (0 °C) solution of *N*-methylmorpholine *N*-oxide (0.009 g, 0.072 mmol) in CH_2Cl_2 (0.3 mL) containing 4 Å molecular sieves. After stirring for 10 min, TPAP (0.001 g, 0.002 mmol) was added and the mixture was stirred at 25 °C for 2.5 h. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with aqueous Na_2SO_3 solution (3×). The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 75:25 hexane/EtOAc) to afford 6.2 mg (36%) of a yellow oil identified as a 5:1 mixture of the 15*E*/15*Z* isomers of aldehyde **33**. Due to its instability, this mixture was used without further purification.

(11′Z)-3,3′-Didehydroxyperidinin (34): Following the general procedure for the modified Julia olefination, the reaction of (a*S*)-**10a** (0.007 g, 0.017 mmol) with a 5:1 15*E*/15*Z* mixture of isomers of aldehyde **33** (0.006 g, 0.017 mmol), NaHMDS (0.044 mL, 1 M in THF, 0.044 mmol) in THF (0.5 mL) for 2 h from −78 °C to 0 °C afforded, after purification by column chromatography (silica gel, 80:20→70:30 hexane/EtOAc), 6.0 mg (63%) of a red solid identified as (11′*Z*)-**34**. ^1H NMR (600 MHz, $(CD_3)_2CO$): $\delta=7.50$ (s, 1H; CH), 7.17 (d, $J=15.6$ Hz, 1H; CH), 7.10 (t, $J=12.8$ Hz, 1H; CH), 6.76 (t, $J=12.3$ Hz, 1H; CH), 6.70–6.60 (m, 2H; CH), 6.47 (t, $J=10.4$ Hz, 1H; CH), 6.42 (d, $J=15.6$ Hz, 1H; CH), 6.22 (t, $J=11.5$ Hz, 1H; CH), 6.18 (s, 1H; CH), 6.0 (s, 1H; CH), 3.54 (s, 1H; OH), 2.21 (d, $J=6.0$ Hz, 3H; CH_3), 2.00 (m, 1H; CH_2), 1.89 (s, 3H; CH_3), 1.90–1.80 (m, 2H; CH_2), 1.60–1.50 (m, 1H; CH_2), 1.50–1.30 (m, 7H; CH_2), 1.36 (s, 3H; CH_3), 1.28 (s, 3H; CH_3), 1.16 (s, 3H; CH_3), 1.13 (s, 3H; CH_3), 1.09 (m, 1H; CH_2), 1.01 (s, 3H; CH_3), 0.91 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta=204.4$ (s), 170.2 (s), 149.1 (s), 139.8 (d), 138.7 (d), 137.9 (s), 135.7 (s), 135.3 (d), 134.1 (d), 131.5 (d), 130.4 (d), 129.6 (d), 126.5 (s), 124.4 (d), 123.6 (d), 121.3 (s), 120.5 (d), 104.4 (d), 72.7 (s), 71.7 (s), 67.3 (s), 42.6 (t), 42.4 (t), 37.5 (t), 36.2 (s), 35.3 (s), 33.6 (q), 32.6 (q), 31.7 (t), 30.2 (q), 27.4 (q), 27.1 (q), 22.0 (q), 20.0 (t), 18.7 (t), 16.5 (q), 15.2 ppm (q); IR (NaCl): $\tilde{\nu}=3600$–3400 (br, OH), 2961 (s, C–H), 2923 (s, C–H), 2849 (m, C–H), 1926 (w, C=C=C), 1749 (s, C=O), 1521 (w), 1449 cm^{-1} (w); MS (FAB^+): m/z (%): 558 $[M+2]^+$ (10), 557 $[M+1]^+$ (11), 556 $[M]^+$ (85), 540 (12), 539 (26), 394 (15), 393 (26), 322 (27), 307 (29), 289 (20), 241 (12), 165 (27); HRMS (FAB^+): m/z: calcd for $C_{37}H_{49}O_4$: 557.3631; found: 557.3613.

(+)-(2*E*)-3-Methyl-5-[(6*R*)-4-(*tert*-butyldimethylsilyloxy)-2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptan-1-yl)pent-2-en-4-yn-1-ol (35c): $[Pd(PPh_3)_4]$ (0.015 g, 0.013 mmol) and CuI (0.003 g, 0.013 mmol) were added to a solution of **13c** (0.383 g, 1.3 mmol) and **36** (0.258 g, 1.3 mmol) in *i*Pr_2NH (7 mL). After stirring for 1 h, a saturated aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O (3×). The combined organic layers were washed with brine (3×), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 80:20 hexane/EtOAc) to afford 0.370 g (78%) of a yellow oil identified as **35c**. $[\alpha]_D^{23}=+36.73$ ($c=0.022$ in MeOH); ^1H NMR (400 MHz, C_6D_6): $\delta=5.94$ (t, $J=6.6$ Hz, 1H; CH), 4.00–3.90 (m, 1H; CH), 3.76 (d, $J=6.5$ Hz, 2H; CH_2), 2.25 (dd, $J=14.4$, 5.1 Hz, 1H; CH_2), 1.67 (dd, $J=14.4$, 7.9 Hz, 1H; CH_2), 1.60–1.50 (m, 1H; CH_2), 1.55 (s, 3H; CH_3), 1.49 (s, 3H; CH_3), 1.36 (s, 3H; CH_3), 1.30 (s, 3H; CH_3), 1.40–1.30 (m, 1H; CH_2), 0.98 (s, 9H; CH_3), 0.05 ppm (s, 6H; CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): $\delta=138.1$ (d), 117.8 (s), 87.8 (s), 83.9 (s), 65.9 (s), 64.3 (d), 63.2 (s), 57.9 (t), 45.2 (t), 40.0 (t), 33.9 (s), 29.0 (q, 2×), 25.2 (q, 3×), 21.0 (q), 17.6 (s), 16.5 (q), −5.6 ppm (q); IR (NaCl): $\tilde{\nu}=3650$–3100 (br, OH), 2956 (s, C–H), 2928 (s, C–H), 2857 (m, C–H), 1636 (w), 1086 cm^{-1} (m); UV (MeOH): $\lambda_{max}=231$ nm; MS (EI^+): m/z (%): 364 $[M]^+$ (1), 235 (11), 233 (40), 219 (15), 217 (71), 173 (20), 163 (12), 160 (16), 159 (20), 157 (14), 145 (23), 143 (26), 142 (11), 141 (14), 131 (15), 129 (19), 128 (14), 121 (11), 119 (13), 117 (10), 115 (34), 105 (29), 91 (36), 77 (22), 75 (100), 73 (89), 69 (14); HRMS (EI^+): m/z: calcd for $C_{21}H_{36}O_3Si$: 364.2434; found: 364.2451.

(−)-(1*R*,5*S*,2a*R*,3′*E*)-5-(*tert*-Butyldimethylsilyloxy)-2-(5-hydroxy-3-methylpenta-1,3-dienylidene)-1,3,3-trimethylcyclohexanol (37c): DIBAL-H (10.14 mL, 1 M in hexane, 10.14 mmol) was added to a solution of **35c** (0.370 g, 1.01 mmol) in CH_2Cl_2 (12 mL) at 0 °C and the mixture was stirred for 10 min. After careful addition of H_2O (5 mL) and a 10% aqueous solution of HCl, the mixture was extracted with EtOAc (3×). The combined organic layers were washed with brine (3×), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, 80:20 hexane/EtOAc) to afford 0.372 mg (100%) of a yellow oil identified as **37c**. $[\alpha]_D^{22}=-24.52$ ($c=0.027$ in MeOH); ^1H NMR (400 MHz, $(CD_3)_2CO$): $\delta=5.91$ (s, 1H; CH), 5.56 (t, $J=6.6$ Hz, 1H; CH), 4.40–4.30 (m, 1H; CH), 4.18 (d, $J=6.0$ Hz, 2H; CH_2), 2.14 (dd, $J=12.7$, 4.1 Hz, 1H; CH_2), 1.84 (dd, $J=12.5$, 4.0 Hz, 1H; CH_2), 1.68 (s, 3H; CH_3), 1.60–1.50 (m, 1H; CH_2), 1.36 (s, 3H; CH_3), 1.40–1.30 (m, 1H; CH_2), 1.31 (s, 3H; CH_3), 1.05 (s, 3H; CH_3), 0.92 (s, 9H; CH_3), 0.11 ppm (s, 6H; CH_3); ^{13}C NMR (100 MHz, $CO(CD_3)_2$): $\delta=202.1$ (s), 132.4 (s), 129.3 (d), 128.8 (s), 102.5 (d), 72.8 (s), 66.3 (d), 59.7 (t), 51.6 (t), 51.5 (t), 36.6 (s), 33.1 (q), 31.8 (q), 29.9 (q), 26.6 (q, 3×), 19.0 (s), 14.1 (q), −4.0 ppm (q, 2×); IR (NaCl): $\tilde{\nu}=3550$–3050 (br, OH), 2956 (s, C–H), 2927 (s, C–H), 2856 (m, C–H), 1937 (w, C=C=C), 1472 (w), 1080 cm^{-1} (m); UV (MeOH): $\lambda_{max}=227$ nm; MS (EI^+): m/z (%): 365 (19), 364 (13), 348 (17), 347 (38), 335 (11), 321 (11), 307 (15), 285 (11), 281 (19), 239 (11), 233 (22), 223 (12), 215 (27), 207 (15), 201 (16), 199 (16), 189 (28), 175 (10), 173 (14), 163 (12), 159 (15), 149 (32), 147 (15), 145 (12), 143 (23), 135 (17), 133 (27), 131 (11), 125 (12), 123 (16), 121 (22), 119 (15), 109 (11), 107 (17), 105 (18), 95 (21), 93 (12), 91 (14), 83 (11), 75 (100), 73 (67), 69 (24); HRMS (EI^+): m/z: calcd for $C_{21}H_{38}O_3Si$: 366.2590; found: 366.2592.

(−)-(1*R*,5*S*,2a*R*,3′*E*)-2-[5-(Benzothiazol-2-yl)-sulfanyl)-3-methylpenta-1,3-dienylidene-5-(*tert*-butyldimethylsilyloxy)-1,3,3-trimethylcyclohexanol (38c): Following the general procedure for sulfide formation, the reaction of **37c** (70 mg, 0.193 mmol) with PPh_3 (0.081 g, 0.309 mmol), DIAD (0.057 mL, 0.289 mmol) and 2-mercaptobenzothiazol (0.049 g, 0.289 mmol) in THF (3 mL) at 0 °C for 1 h afforded, after purification by column chromatography (silica gel, 80:20 hexane/EtOAc), 0.104 g (100%) of a yellow oil identified as **38c**. $[\alpha]_D^{23}=-39.65$ ($c=0.023$ in MeOH); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.89$ (d, $J=8.1$ Hz, 1H; ArH), 7.77 (d, $J=7.9$ Hz, 1H; ArH), 7.43 (t, $J=8.2$ Hz, 1H; ArH), 7.40–7.30 (m, 1H; ArH), 5.95 (s, 1H; CH), 5.64 (t, $J=7.8$ Hz, 1H; CH), 4.30–4.20 (m, 1H; CH), 4.13 (d, $J=8.0$ Hz, 2H; CH_2), 2.15 (dd, $J=13.1$, 4.0 Hz, 1H; CH_2), 1.83 (dd, $J=12.6$, 3.9 Hz, 1H; CH_2), 1.77 (s, 3H; CH_3), 1.50–1.40 (m, 1H; CH_2), 1.33 (s, 6H; CH_3), 1.30–1.20 (m, 1H; CH_2), 1.05 (s, 3H; CH_3), 0.93 (s, 9H; CH_3), 0.12 ppm (s, 6H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.4$ (s), 166.4 (s), 153.3 (s), 135.6 (s), 133.8 (d), 128.7 (s), 126.0 (d), 124.2 (d), 121.5 (d), 120.9 (d), 118.0 (s), 101.6 (d), 72.9 (s), 64.9 (d), 49.9 (t), 49.2 (t), 35.6 (s), 32.2 (t), 32.1 (q), 32.4 (q), 29.3 (q, 3×), 25.9 (q), 18.2 (s), 13.6 (q), −4.6 ppm (q, 2×); IR (NaCl): $\tilde{\nu}=$ 3500–3100 (br, OH), 2955 (s, C–H), 2926 (s, C–H), 2854 (m, C–H), 1936 (w, C=C=C), 1457 (s), 1427 (s), 1077 cm^{-1} (s); UV (MeOH): $\lambda_{max}=$ 228 nm; MS (EI^+): m/z (%): 515 $[M]^+$ (16), 330 (10), 291 (22), 199 (13), 173 (11), 168 (14), 167 (52), 159 (28), 149 (16), 135 (44), 134 (14), 133 (100), 105 (22), 95 (71), 93 (15); HRMS (EI^+): m/z: calcd for $C_{28}H_{41}NO_2SiS_2$: 515.2348; found: 515.2362.

(−)-(1*S*,3*R*,4a*R*,3′*E*)-4-[5-(Benzothiazol-2-yl)-sulfanyl)-3-methylpenta-1,3-dienylidene]-3-hydroxy-3,5,5-trimethylcyclohexyl acetate (38d): Formic acid (5.7 mL) and H_2O (1.90 mL) were added to a solution of **38c** (0.0541 g, 0.105 mmol) in THF (11.4 mL). After stirring for 2 h, the mixture was cooled down to 0 °C, neutralized with $NaHCO_3$ and extracted with AcOEt (3×). The combined organic layers were dried and the solvent was removed. The residue was used without further purification. Acetic anhydride (0.041 mL) was then added to a solution of this residue in pyridine (1.4 mL) and the mixture was stirred overnight. A saturated aqueous solution of $CuSO_4$ was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with a saturated aqueous solution of $CuSO_4$ (3×), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, 80:20 hexane/EtOAc) to afford 0.046 mg (99%) of a yellow oil identified as **38d**. $[\alpha]_D^{23}=-22.52$ ($c=0.05$ in MeOH); ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.89 (d, $J=8.1$ Hz, 1H; ArH), 7.77 (d, $J=7.9$ Hz, 1H; ArH), 7.43 (t, $J=$ 8.2 Hz, 1H; ArH), 7.32 (t, $J=7.3$ Hz, 1H; ArH), 5.98 (s, 1H; CH), 5.65

(t, $J=7.9$ Hz, 1H; CH), 5.39 (t, $J=7.2$ Hz, 1H; CH), 4.13 (d, $J=8.0$ Hz, 2H; CH_2), 2.29 (dd, $J=12.8$, 4.0 Hz, 1H; CH_2), 2.05 (s, 3H; CH_3), 2.00 (dd, $J=12.3$, 4.0 Hz, 1H; CH_2), 1.78 (s, 3H; CH_3), 1.30–1.20 (m, 1H; CH_2), 1.38 (s, 3H; CH_3), 1.34 (s, 3H; CH_3), 1.30–1.20 (m, 1H; CH_2), 1.07 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.3$ (s), 170.4 (s), 166.3 (s), 153.2 (s), 135.4 (s), 135.2 (s), 126.0 (d), 124.3 (d), 121.5 (d), 121.1 (d), 120.9 (d), 117.5 (s), 101.8 (s), 72.5 (s), 67.9 (d), 45.4 (t), 45.2 (t), 35.6 (s), 32.1 (t), 32.0 (q), 31.2 (q), 29.1 (q), 21.4 (q), 13.6 ppm (q); IR (NaCl): $\tilde{\nu}=3700$–3100 (br, OH), 2964 (s, C–H), 2924 (s, C–H), 1938 (w, C=C=C), 1729 (s, C=O), 1427 (s), 1250 cm^{-1} (s); UV (MeOH): $\lambda_{max}=227$, 281, 301 nm; MS (EI$^+$): m/z (%): 183 (17), 167 (100), 145 (10), 143 (10), 121 (18), 115 (10), 108 (12), 105 (18), 95 (29), 91 (23); HRMS (EI$^+$): m/z: calcd for $C_{24}H_{29}NO_3S_2$: 443.1589; found: 443.1607.

(+)-(1*S*,3*R*,4a*R*,3′*E*)-4-(-5-(Benzothiazol-2-yl)-sulfanyl)-3-methylpenta-1,3-dienylidene)-3-hydroxy-3,5,5-trimethylcyclohexyl formate (38e): $[\alpha]_D^{23}=+24.25$ ($c=0.024$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 8.05 (s, 1H; CH), 7.87 (d, $J=8.1$ Hz, 1H; ArH), 7.75 (d, $J=8.8$ Hz, 1H; ArH), 7.14 (t, $J=7.3$ Hz, 1H; ArH), 7.23 (t, $J=7.2$ Hz, 1H; ArH), 5.96 (s, 1H; CH), 5.64 (t, $J=7.9$ Hz, 1H; CH), 5.50–5.40 (m, 1H; CH), 4.12 (d, $J=8.0$ Hz, 2H; CH_2), 2.29 (dd, $J=12.8$, 4.1 Hz, 1H; CH_2), 2.02 (dd, $J=12.3$, 3.9 Hz, 1H; CH_2), 1.76 (s, 3H; CH_3), 1.50–1.40 (m, 1H; CH_2), 1.37 (s, 3H; CH_3), 1.33 (s, 3H; CH_3), 1.30–1.20 (m, 1H; CH_2), 1.06 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.3$ (s), 166.3 (s), 160.5 (d), 153.2 (s), 135.4 (s), 135.1 (s), 126.0 (d), 124.3 (d), 121.5 (d), 121.3 (d), 121.0 (d), 117.4 (s), 101.9 (d), 72.5 (s), 68.1 (d), 45.3 (t), 45.1 (t), 35.6 (s), 32.1 (t), 32.0 (q), 31.1 (q), 29.2 (q), 13.6 ppm (q); IR (NaCl): $\tilde{\nu}=3550$–3000 (br, OH), 2963 (s, C–H), 2925 (s, C–H), 2857 (m, C–H), 1938 (w, C=C=C), 1721 (s, C=O), 1457 (s), 1427 (s), 1160 cm^{-1} (s); UV (MeOH): $\lambda_{max}=227$, 301 nm; MS (EI$^+$): m/z (%): 429 $[M]^+$ (1), 166 (100), 159 (12), 135 (13), 108 (12), 105 (22), 95 (21), 91 (29); HRMS (EI$^+$): m/z: calcd for $C_{23}H_{27}NO_3S_2$: 429.1432; found: 429.1418.

(−)-(1*S*,3*R*,3′*E*)-4-[5-(benzothiazol-2-yl)sulfonyl-3-methylpenta-1,3-dienylidene)-3-hydroxy-3,5,5-trimethylcyclohexyl acetate ((a*R*)-10d): Following the general procedure for sulfone formation, the reaction at −10 °C of **38b** (0.081 g, 0.183 mmol) in EtOH (9.3 mL) with $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (0.045 g, 0.036 mmol) in 35% H_2O_2 (0.235 mL, 2.74 mmol) for 16 h afforded, after purification by column chromatography (silica gel, 70:30 hexane/EtOAc), 0.08 g (93%) of a white solid identified as (a*R*)-**10d**. $[\alpha]_D^{21}=-33.18$ ($c=0.033$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.20$ (d, $J=7.7$ Hz, 1H; ArH), 7.97 (d, $J=7.8$ Hz, 1H; ArH), 7.60–7.50 (m, 2H; ArH), 5.91 (s, 1H; CH), 5.42 (t, $J=8.0$ Hz, 1H; CH), 5.40–5.20 (m, 1H; CH), 4.32 (d, $J=8.1$ Hz, 2H; CH_2), 2.19 (dd, $J=12.8$, 4.0 Hz, 1H; CH_2), 2.00 (s, 3H; CH_3), 1.90 (dd, $J=12.3$, 3.9 Hz, 1H; CH_2), 1.48 (s, 3H; CH_3), 1.40–1.30 (m, 1H; CH_2), 1.30 (s, 3H; CH_3), 1.30–1.20 (m, 1H; CH_2), 1.13 (s, 3H; CH_3), 0.84 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.8$ (s), 170.4 (s), 165.6 (s), 152.6 (s), 141.0 (s), 137.1 (s), 128.0 (d), 127.7 (d), 125.4 (d), 122.3 (d), 117.8 (s), 111.0 (d), 101.3 (d), 72.3 (s), 67.8 (d), 55.4 (t), 45.2 (t), 45.1 (t), 35.5 (s), 31.7 (q), 30.9 (q), 29.0 (q), 21.3 (q), 13.8 ppm (q); IR (NaCl): $\tilde{\nu}=3600$–3300 (br, OH), 2965 (s, C–H), 2925 (s, C–H), 1939 (w, C=C=C), 1729 (s, C=O), 1328 (s), 1252 cm^{-1} (s); UV (MeOH): $\lambda_{max}=242$, 288 nm; MS (FAB$^+$): m/z (%): 476 $[M+1]^+$ (5), 308 (11), 307 (42), 289 (19), 282 (14); HRMS (FAB$^+$): m/z: calcd for $C_{24}H_{30}NO_5S_2$: 476.1565; found: 476.1553.

(−)-(1*S*,3*R*,4a*R*,3′*E*,5′*Z*,7′*E*)-3-Methyl-4-[8-(tributyltin)octa-1,3,5,7-tetraenylidene]-3-hydroxy-3,5,5-trimethylcyclohexyl acetate ((a*R*,5′*Z*)-8): Following the general procedure for the Julia olefination, (a*R*)-**10** (0.033 g, 0.069 mmol) was reacted with **9** (0.036 g, 1.03 mmol) and NaHMDS (0.207 mL, 1 M in THF, 0.207 mmol) in THF (5.2 mL) for 3 h at −78 °C. Purification of the crude by column chromatography (silica gel, 90:7:3 hexane/EtOAc/Et_3N), 0.0327 mg (78%) afforded a yellow oil, which was identified as (a*R*,5′*Z*)-**8**. $[\alpha]_D^{27}=-59.2$ ($c=0.02$ in MeOH); ^{1}H NMR (400 MHz, C_6D_6): $\delta=7.46$ (dd, $J=18.5$, 9.9 Hz, 1H; CH), 6.78 (d, $J=10.1$ Hz, 1H; CH), 6.56 (d, $J=18.5$ Hz, 1H; CH), 6.27 (t, $J=$ 11.0 Hz, 1H; CH), 6.21 (t, $J=10.5$ Hz, 1H; CH), 5.95 (s, 1H; CH), 5.68 (ddd, $J=11.5$, 7.2, 4.1 Hz, 1H; CH), 2.28 (ddd, $J=12.3$, 3.9, 2.0 Hz, 1H; CH_2), 2.03 (ddd, $J=12.1$, 3.5, 1.8 Hz, 1H; CH_2), 1.75 (s, 3H; CH_3), 1.68 (s, 3H; CH_3), 1.70–1.50 (m, 6H; CH_2), 1.41 (s, 3H; CH_3), 1.40–1.30 (m, 8H; CH_2), 1.14 (s, 3H; CH_3), 1.10–1.00 (m, 6H; CH_2), 1.03 (s, 3H; CH_3), 1.00–0.90 ppm (m, 9H; CH_3); ^{13}C NMR (100 MHz, C_6D_6): $\delta=202.1$ (s), 169.1 (s), 142.3 (d), 136.1 (d), 132.7 (s), 131.8 (d), 124.4 (d), 123.0 (d), 117.6 (s), 103.0 (d), 71.9 (s), 67.6 (d), 45.6 (t), 45.4 (t), 35.5 (s), 31.9 (q), 30.7 (q), 29.2 (t), 28.9 (q), 27.3 (t), 20.6 (q), 13.6 (q), 13.3 (q), 9.6 ppm (t); IR (NaCl): $\tilde{\nu}=3346$ (w), 3205 (w), 2956 (s, C–H), 2917 (s, C–H), 2848 (s, C–H), 1930 (w, C=C=C), 1724 (m, C=O), 1666 (m), 1631 (m), 1462 cm^{-1}(w); UV (MeOH): $\lambda_{max}=306$, 319, 334 nm; MS (FAB$^+$): m/z (%): 549 $[M]^+$ (30), 548 (14), 547 (23), 546 (1), 545 (14), 473 (11), 471 (14), 295 (19), 293 (49), 292 (20), 291 (74), 290 (28), 289 (56), 288 (16), 287 (25), 251 (11), 249 (10), 239 (26), 237 (24), 235 (43), 234 (16), 233 (34), 232 (14), 231 (22), 223 (10), 207 (11), 183 (23), 181 (23), 179 (100), 178 (31), 177 (96), 176 (33), 175 (64), 173 (17), 171 (12), 157 (12), 155 (11), 154 (11); HRMS (FAB$^+$): m/z: calcd for $C_{28}H_{45}O_3{}^{116}Sn$: 545.2386; found: 545.2388; calcd for $C_{28}H_{45}O_3{}^{120}Sn$: 549.2391; found: 549.2395.

Peridinin (1): Following the general procedure for the Stille cross-coupling, the reaction of (a*R*,5′*Z*)-**8** (0.013 g, 0.021 mmol) with **6** (0.006 g, 0.018 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.0004 g, 0.0004 mmol), $[AsPh_3]$ (0.009 g, 0.0028 mmol) and $Bu_4NPh_2PO_2$ (0.0097 g, 0.021 mmol) in THF (0.4 mL) for 4 h at 25 °C afforded, after purification by column chromatography (silica gel, 80:20 hexane/EtOAc), 6 mg (65%) of a red solid identified as a mixture of (a*R*,11′*E*)-**29a** and (a*R*,11′*Z*)-**29a** in a 1:3 ratio, which was used immediately. Following the general procedure for the Stille cross-coupling, the reaction of **29a** (0.006 g, 0.011 mmol) with **7b** (0.006 g, 0.014 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.0007 g, 0.0007 mmol), $[AsPh_3]$ (0.0017 g, 0.0054 mmol) and $Bu_4NPh_2PO_2$ (0.0052 g, 0.011 mmol) in THF (0.52 mL) for 19 h at 55 °C afforded, after purification by column chromatography (silica gel, 90:10→80:20 hexane/acetone), 4.8 mg (69%) of a red solid identified as peridinin (**1**). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=$ 7.16 (d, $J=15.6$ Hz, 1H; CH), 7.01 (s, 1H; CH), 6.62 (dd, $J=15.2$, 11.9 Hz, 1H; CH), 6.61 (dd, $J=15.2$, 11.9 Hz, 1H; CH), 6.50 (dd, $J=$ 14.2, 11.1 Hz, 1H; CH), 6.44 (d, $J=11.5$ Hz, 1H; CH), 6.40 (dd, $J=14.5$, 10.5 Hz, 1H; CH), 6.36 (d, $J=15.6$ Hz, 1H; CH), 6.10 (d, $J=11.8$ Hz, 1H; CH), 6.04 (s, 1H; CH), 5.72 (s, 1H; CH), 5.40–5.30 (m, 1H; CH), 3.90–3.80 (m, 1H; CH), 2.39 (ddd, $J=14.4$, 4.9, 1.9 Hz, 1H; CH_2), 2.27 (ddd, $J=12.7$, 3.9, 1.7 Hz, 1H; CH_2), 2.22 (s, 3H; CH_3), 2.03 (s, 3H; CH_3), 1.98 (ddd, $J=12.3$, 4.1, 1.8 Hz, 1H; CH_2), 1.79 (s, 3H; CH_3), 1.63 (dd, $J=14.2$, 8.9 Hz, 1H; CH_2), 1.62 (d, $J=14.4$ Hz, 1H; CH_2), 1.50–1.40 (m, 1H; CH_2), 1.40–1.30 (m, 1H; CH_2), 1.37 (s, 3H; CH_3), 1.34 (s, 3H; CH_3), 1.30–1.20 (m, 1H; CH_2), 1.20 (s, 3H; CH_3), 1.19 (s, 3H; CH_3), 1.06 (s, 3H; CH_3), 0.97 (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=202.6$ (s), 170.4 (s), 168.7 (s), 146.8 (s), 138.0 (d), 137.2 (d), 136.3 (d), 134.0 (s), 133.9 (s), 133.6 (d), 133.0 (d), 131.5 (d), 128.9 (d), 128.1 (d), 124.8 (s), 121.8 (d), 119.2 (d), 117.6 (s), 103.3 (d), 72.7 (s), 70.4 (s), 67.5 (d), 67.3 (s), 64.2 (d), 47.1 (t), 45.4 (t), 45.2 (t), 40.9 (t), 35.8 (s), 35.3 (s), 32.0 (q), 31.3 (q), 29.5 (q), 29.2 (q), 24.9 (q), 21.4 (q), 19.9 (q), 15.4 (q), 14.0 ppm (q); IR (NaCl): $\tilde{\nu}=3600$–3300 (br, OH), 2961 (s, C–H), 2925 (s, C–H), 1927 (w, C=C=C), 1748 cm^{-1} (s, C=O); MS (FAB$^+$): m/z (%): 631 $[M+1]^+$ (12), 630 $[M]^+$ (25), 391 (20), 307 (14); HRMS (FAB$^+$): m/z: calcd for $C_{39}H_{50}O_7$: 630.3557; found: 630.3572; calcd for $C_{39}H_{51}O_7$: 631.3635; found: 631.3627.

(2*E*,4*E*,6*Z*)-6-[4-Bromo-5-oxofuran-2(5*H*)-ylidene]-5-methylhexa-2,4-dienal (39): MnO_2 (0.43 g, 4.94 mmol) and Na_2CO_3 (0.52 g, 4.94 mmol) were added to a cooled (0 °C) solution of **15** (0.074 g, 0.27 mmol) in CH_2Cl_2 (6.4 mL) and the suspension was stirred for 2 h. The mixture was filtered through Celite and the solvent was removed. The residue was purified by column chromatography (silica gel, 70:30 hexane/EtOAc) to afford 0.053 g (72%) of a yellow oil identified as **39**. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.65$ (d, $J=7.8$ Hz, 1H; CH), 7.47 (s, 1H; CH), 7.45 (dd, $J=$ 15.0, 11.7 Hz, 1H; CH), 6.60 (d, $J=11.7$ Hz, 1H; CH), 6.27 (dd, $J=15.0$, 7.8 Hz, 1H; CH), 5.79 (s, 1H; CH), 2.33 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=193.3$ (d), 164.9 (s), 148.6 (s), 145.6 (d), 142.4 (d), 142.3 (s), 134.7 (d), 133.8 (d), 117.6 (d), 112.6 (s), 16.1 ppm (q); MS (EI$^+$): m/z (%): 293 $[M+23]^+$ (75), 291 $[M+23]^+$ (77), 285 (16), 279 (27), 279 (15), 271 $[M+1]^+$ (97), 269 $[M+1]^+$ (100), 247 (15); HRMS (EI$^+$): m/z: calcd for $C_{11}H_{10}{}^{79}BrO_3$: 268.9808; found: 268.9797; calcd for $C_{11}H_{10}{}^{81}BrO_3$: 270.9707; found: 268.9776.

Apo-peridinin-14′-al (40): Following the general procedure for the Stille cross-coupling, the reaction of **39** (0.040 g, 0.149 mmol) with **7b** (0.084 g,

0.179 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.008 g, 0.007 mmol), $Bu_4NPh_2PO_2$ (0.082 g, 0.179 mmol) and BHT (traces) in DMF (6 mL) for 4 h at 60 °C, afforded, after purification by column chromatography (silica gel, 60:40→50:50 hexane/EtOAc) 35 mg (64 %) of a yellow oil identified as **40**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (d, J = 7.9 Hz, 1H; CH), 7.46 (dd, J = 15.0, 11.5 Hz, 1H; CH), 7.22 (d, J = 15.5 Hz, 1H; CH), 7.02 (s, 1H; CH), 6.55 (d, J = 11.8 Hz, 1H; CH), 6.37 (d, J = 15.6 Hz, 1H; CH), 6.22 (dd, J = 15.2, 7.9 Hz, 1H; CH), 5.71 (s, 1H; CH), 3.90–3.80 (m, 1H; CH), 2.36 (dd, J = 14.3, 5.0 Hz, 1H; CH_2), 2.31 (s, 3H; CH_3), 1.60–1.50 (m, 2H; CH_2), 1.30 (dd, J = 14.8, 7.4 Hz, 1H; CH_2), 1.18 (s, 3H; CH_3), 1.16 (s, 3H; CH_3), 0.94 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3 (d), 167.8 (s), 149.4 (s), 146.0 (d), 143.1 (s), 136.0 (d), 135.7 (d), 133.1 (d), 132.9 (d), 127.2 (s), 121.3 (d), 116.5 (d), 70.3 (s), 67.5 (s), 64.0 (d), 46.8 (t), 40.7 (t), 35.2 (s), 29.3 (q), 24.8 (q), 19.7 (q), 16.1 ppm (q); MS (EI$^+$): m/z (%): 372 $[M+2]^+$ (22), 371 $[M+1]^+$ (100), 340 (16), 315 (17), 279 (17); HRMS (EI$^+$): m/z: calcd for $C_{22}H_{27}O_5$: 371.1853; found: 371.1848.

11′*Z*-Peridinin (11′*Z*-1): Following the general procedure for the Julia olefination, the reaction of (a*R*)-**10d** (0.019 g, 0.039 mmol) with **40** (0.018 g 0.047 mmol), NaHMDS (0.118 mL, 1 M in THF, 0.118 mmol) and BHT (traces) in THF (3.1 mL) for 6 h from −78 °C to −30 °C afforded, after purification by column chromatography (silica gel, 80:20→70:30 hexane/EtOAc), 0.0132 mg (53 %) of a red solid identified as (11′*Z*)-peridinin (**1**). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.19 (d, J = 15.6 Hz, 1H; CH), 7.03 (s, 1H; CH), 6.95 (t, J = 13.1 Hz, 1H), 6.65 (dd, J = 13.9, 12.1 Hz, 1H), 6.60–6.50 (m, 2H; CH), 6.40 (d, J = 15.7 Hz, 1H; CH), 6.40–6.30 (m, 1H; CH), 6.17 (t, J = 11.7 Hz, 1H; CH), 6.12 (s, 1H; CH), 5.75 (s, 1H; CH), 5.40–5.30 (m, 1H; CH), 3.91 (s, 1H; CH), 2.32 (dd, J = 14.3, 4.4 Hz, 1H; CH_2), 2.22 (dd, J = 12.0, 3.5 Hz, 1H; CH_2), 2.03 (s, 3H; CH_3), 2.00–1.90 (m, 1H; CH_2), 1.82 (s, 3H; CH_3), 1.70–1.60 (m, 2H; CH_2), 1.60–1.40 (m, 2H; CH_2), 1.40 (s, 3H; CH_3), 1.36 (s, 3H; CH_3), 1.30–1.20 (m, 1H; CH_2), 1.20 (s, 3H; CH_3), 1.19 (s, 3H; CH_3), 1.08 (s, 3H; CH_3), 0.98 ppm (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7 (s), 170.4 (s), 168.7 (s), 146.9 (s), 137.8 (d), 136.3 (d), 134.4 (s), 134.3 (s), 133.8 (d), 131.8 (d), 129.9 (d), 129.2 (d), 127.4 (d), 124.0 (s), 123.1 (d), 121.8 (d), 119.0 (d), 117.7 (s), 103.5 (d), 72.7 (s), 70.5 (s), 67.9 (d), 67.8 (s), 64.2 (d), 47.1 (t), 45.4 (t), 45.2 (t), 40.9 (t), 35.8 (s), 35.3 (s), 32.0 (q), 31.3 (q), 29.5 (q), 27.5 (q), 24.9 (q), 21.4 (q), 19.9 (q), 15.5 (q), 13.7 ppm (q); IR (NaCl): $\tilde{\nu}$ = 3600–3300 (br, OH), 2961 (s, C−H), 2924 (s, C−H), 2852 (m, C−H), 1928 (w, C=C=C), 1748 cm^{-1} (s, C=O); MS (FAB$^+$): m/z (%): 631 $[M+1]^+$ (17), 630 $[M]^+$ (32), 553 (11), 491 (17), 90 (14), 415 (11), 413 (12), 392 (21), 391 (65), 389 (10), 371 (14), 359 (18), 358 (45), 357 (10), 355 (16), 343 (13), 341 (13), 329 (14), 328 (20), 327 (21), 326 (77), 325 (12), 324 (13); HRMS (FAB$^+$): m/z: calcd for $C_{39}H_{50}O_7$: 630.3557; found: 630.3567; calcd for $C_{39}H_{51}O_7$: 631.3635; found: 631.3617.

Peridinin (1): $[Pd_2(dba)_3]\cdot CHCl_3$ (0.0005 g, 0.0005 mmol) and $[AsPh_3]$ (0.0012 g, 0.004 mmol) were added to a solution of (11′*Z*)-peridinin (**1**) (0.0024 g, 0.0038 mmol) in THF (0.100 mL). After stirring for 7 h at 25 °C, brine was added and the mixture was extracted with EtOAc/CH_2Cl_2 (90:10) (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 90:10→80:20 hexane/acetone) to afford 2 mg (83 %) of a red solid identified as peridinin (**1**).

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