Carotenoids and related polyenes. Part 6.[1] Stereoselective synthesis of astaxanthin analogues and their antioxidant activities

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Astaxanthin analogues having various lengths of polyene chains are stereoselectively synthesized and their singlet-oxygen-quenching activities are examined.

Introduction

Carotenoid pigments are widely distributed in Nature, where they play an important role in protecting cells and organisms against photosensitized oxidation.[2]

Astaxanthin **1** (Fig. 1), one of the dominant carotenoids in marine animals, has become the center of attention due to its extremely strong antioxidant activities.[3] These strong activities are considered[3] to be profoundly related to the 3-hydroxy-4-oxo-β-end-groups† conjugated to the polyene system in astaxanthin. Antioxidant activity should be also concerned with the length of the conjugated double-bond system in carotenoids. Thus, in order to clarify their structure–activity relationships, especially the relationship between the activity and the length of the conjugated double-bond system, we have synthesized astaxanthin analogues **2a**–**d** having various polyene chains and examined their quenching activities against singlet oxygen. These analogues were stereoselectively synthesized using the C_{15}-building block **3** or **4b**, both of which were prepared in a stereoselective manner *via* the palladium-catalyzed reaction of the vinylstannane **9** or the terminal alkyne **6** with the readily available[4] vinyl bromide **10** (Schemes 1 and 2).

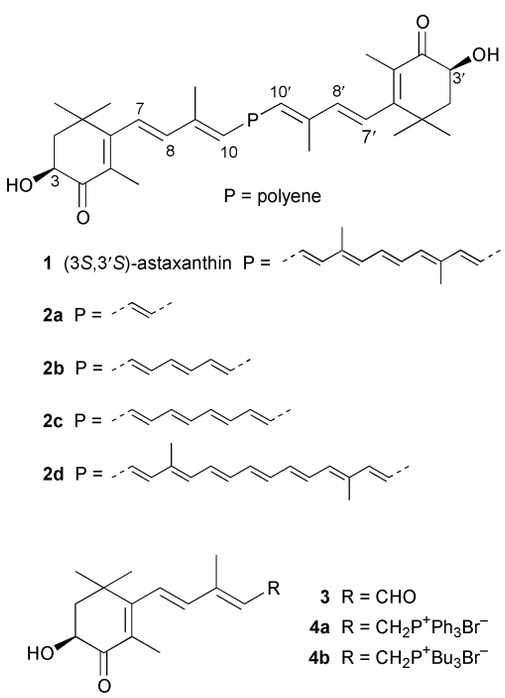

Fig. 1

† We have employed the numbering system used in the carotenoids.

Results and discussion

Synthesis of 3 and 4 *via* Stille coupling reaction

Treatment of the known ketone **5**[5] with lithium trimethylsilyl(TMS)acetylide followed by deprotection afforded the terminal alkyne **6** as a single product[6] in 98% yield (Scheme 1). Heating the alkyne **6** at 120 °C for 2 h with 1.5 equiv. of tri-*n*-butyltin hydride in the presence of a catalytic amount of azoisobutyronitrile (AIBN)[7] provided a mixture of the *E*-vinylstannane **7a** (40%) and its *Z*-isomer **7b** (38%), which were cleanly separated by column chromatography. The *Z*-isomer **7b** was converted to a mixture of **7a** (67%) and **7b** (22%) by treatment with tri-*n*-butyltin hydride under the same conditions. On the other hand, the palladium-catalyzed hydrostannylation[7] of the alkyne **6** predominantly provided *E*-vinylstannane **7a** in 68% yield which, on treatment with acid (92%) followed by acetylation (97%), was converted to compound **9** *via* **8**. The regio- and stereochemical structures of these vinylstannanes **7a**, **7b**, **8** and **9** were deduced from ^{1}H NMR data (see Experimental section), especially from coupling patterns J_{HH}, $J(^{117}SnH)$, $J(^{119}SnH)$ of the vinylic protons.[7,8]

Among vinylstannanes **7a**, **8** and **9**, only the acetate **9** reacted with the vinyl bromide **10**[4] under the standard conditions reported by Stille[9] (Table 1, run 2) to yield the desired coupled product **11**, stereoselectively. However, in this reaction, homodimer **12** was a major product, even though the reaction flask and solvent were carefully deoxygenated. Thus, the reaction conditions (catalyst, ligand, and solvent) were next examined (Table 1). $Pd(PPh_3)_4$ was not effective for this coupling reaction (run 1). Moderate yields of **11** were achieved by use of tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) in *N*-methylpyrrolidin-2-one (NMP) (run 5) or by combined use of Pd_2dba_3 and $AsPh_3$ (ligand)[10] in either DMF or NMP (run 6, 7). Oxidation of **11** with active MnO_2 (72%) and subsequent methanolysis (81%) afforded the C_{15}-aldehyde **3** without stereomutation. Direct methanolysis of **11** provided C_{15}-alcohol **14** (57%), which was allowed to react with hydrogen bromide[11]

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Table 1 Coupling reaction of the vinylstannane **9** with the vinyl bromide **10**[a]

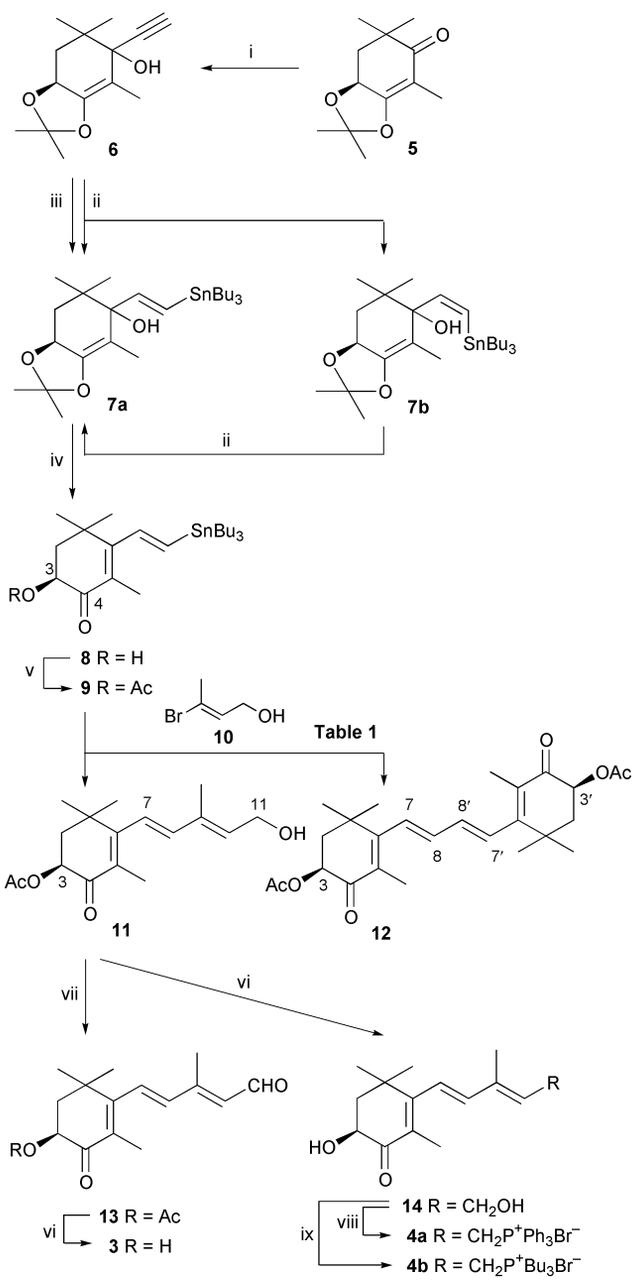
Run	Catalyst(mol%)	Conditions	Yield/%[b] **11**	**12**
1	$Pd(PPh_3)_4$ (3)	DMF, rt, 24 h		
2	$PdCl_2(MeCN)_2$ (10)	DMF, rt, 24 h	20	25
3	$PdCl_2(MeCN)_2$ (6)	NMP, 50 °C, 24 h	20	29
4	Pd_2dba_3 (3)	DMF, 50 °C, 24 h	19	
5	Pd_2dba_3 (3)	NMP, 50 °C, 24 h	46	
6	Pd_2dba_3 (3), $AsPh_3$ (24)	DMF, 50 °C, 24 h	55	17
7	Pd_2dba_3 (3), $AsPh_3$ (24)	NMP, 50 °C, 24 h	54	22

[a] 2 equiv. of vinyl bromide **10** were used. [b] Isolated yield.

Table 2 Coupling reaction of terminal alkyne **15** with the vinyl bromide **10**[a]

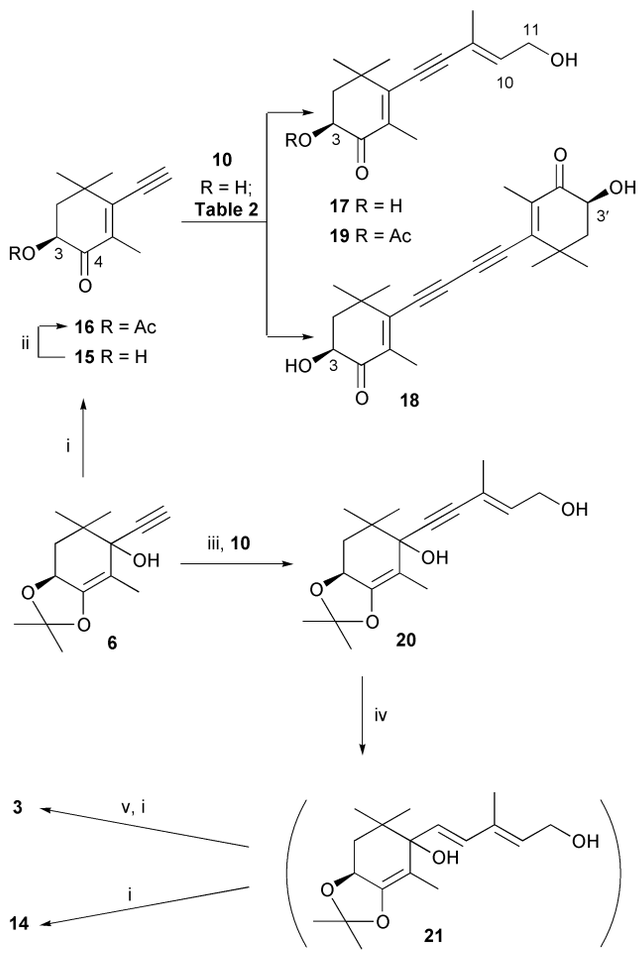
Run	Modification	Yield/%[b] **17**	**18**
1	none	46	43
2	BHT (20 mol%)	46	43
3	degassing	67	33
4	degassing + BHT (5 mol%)	76	24
5	degassing + BHT (10 mol%)	70	30

[a] The reaction was carried out at rt in benzene using 4.5 mol% of $Pd(PPh_3)_4$ and 24 mol% of CuI as catalysts in the presence of Et_2NH (2.3 equiv.). 1.5 equiv. of vinyl bromide **10** were used. [b] Isolated yield.



Scheme 1 *Reagents and conditions*: i, *n*-BuLi, TMS-acetylene; then 10% KOH: ii, Bu_3SnH, cat. AIBN, 120 °C; iii, Bu_3SnH, cat. $PdCl_2(PPh_3)_2$; iv, aq. H_2SO_4; v, Ac_2O, Py; vi, cat. NaOMe, MeOH; vii, MnO_2; viii, 48% HBr; then PPh_3; ix, 48% HBr; then PBu_3.

followed by treatment of the intermediate bromide with triphenylphosphine[11] or tri-*n*-butylphosphine to give the C_{15}-Wittig salt **4a**[11] or **4b**, respectively.



Scheme 2 *Reagents and conditions*: i, aq. H_2SO_4; ii, Ac_2O, Py; iii, cat. $Pd(PPh_3)_4$, Et_2NH, CuI, BHT, degassing; iv, $LiAlH_4$, cat. NaOMe; v, MnO_2.

Synthesis of 3 and 4 *via* Sonogashira coupling reaction

We first investigated the Sonogashira coupling[12] of the terminal alkyne **15** (Scheme 2), prepared (84%) by acid hydrolysis of **6**, with the vinyl bromide **10** (Table 2). Coupling reaction between **15** and **10** by use of $Pd(PPh_3)_4$ (4.5 mol%) and CuI (24 mol%) in the presence of Et_2NH (2.3 equiv.) in benzene gave the cross-coupling product **17**,[11] accompanied by a serious amount of the alkyne dimer **18** (run 1). Negishi[13] described how either degassing *via* freeze–thaw cycles or addition of an antioxidant such as 2,6-*tert*-butyl-4-methylphenol (BHT) was effective in the formation of cross-coupling products. In our case, addition of BHT was not so effective (run 2), but degassing apparently improved the yield of **17** (run 3). The best conditions were obtained by degassing in the presence of BHT (5 mol%) (run 4). On the other hand, coupling reaction of the acetate **16** with **10**

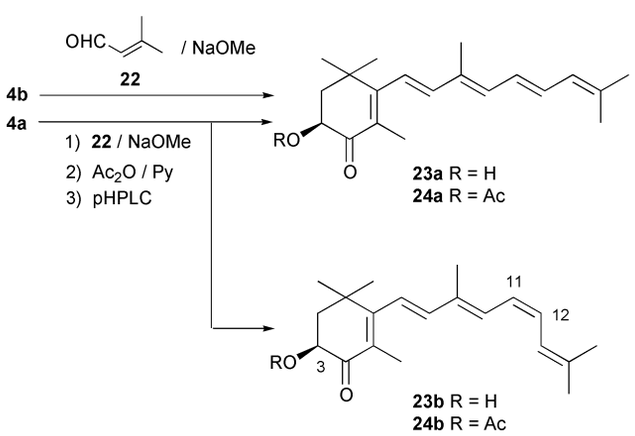
under the optimized conditions yielded the cross-coupling product **19** in high yield (95%) as the sole product. Thus, the hydroxy group at the C-3 position of the alkyne **15** might cause the side reaction.

Then, the alkyne **6** reacted with **10** under the optimized conditions to give the cross-coupling product **20** in 86% yield. This α-acetylenic alcohol **20** was then stereoselectively converted to the C_{15}-aldehyde **3** (83% from **20** *via* **21**) and the alcohol **14** (65% from **20**) *via* hydroalumination using $LiAlH_4$ in the presence of 10 mol% of sodium methoxide.[14] The alcohol **14** could be converted to the C_{15}-Wittig salts **4a**,**b** as shown in Scheme 1.

Synthesis of astaxanthin analogues 2a–d

The C_{15}-triphenylphosphonium salt **4a** (Fig. 1) was previously prepared[11] in the synthesis of astaxanthin **1**. Wittig condensation of the phosphonium salt **4a** with 2,7-dimethylocta-2,4,6-triene-1,8-dial was conducted[11] to give a mixture of *E*/*Z*-isomers of astaxanthin, from which the all-*E*-isomer has been isolated by isomerization and crystallization. It was reported[15] that Wittig reaction of aldehydes with tri-*n*-butylphosphonium salts provided dominantly *E*-olefins. Thus, Wittig reaction of the aldehyde **22** with the phosphonium salts **4a** and **4b** was carried out as a preliminary experiment.

The triphenylphosphonium salt **4a** was condensed with the aldehyde **22** in the presence of sodium methoxide as a base to provide a non-separable mixture of isomers **23a** and **23b** in 85% yield (Scheme 3). This mixture was acetylated to afford the



Scheme 3

acetates **24**, which could be cleanly separated by preparative HPLC (pHPLC) to give the all-*E*-isomer **24a** (22% from **22**) and the 11*Z*-one **24b** (22% from **22**). In contrast, Wittig condensation of the tri-*n*-butylphosphonium salt **4b** with the aldehyde **22** stereoselectively afforded the all-*E*-pentaenone **23a** in 73% yield. Therefore, the tri-*n*-butylphosphonium salt **4b** and bis-(tri-*n*-butylphosphonium) salts **25**[15a] and **26** were used for the preparation of astaxanthin analogues **2a**–**d** (Fig. 1) as shown in Scheme 4.

The analogue **2a** was synthesized (70%) by Wittig reaction between the C_{15}-aldehyde **3** and the C_{15}-phosphonium salt **4b**. Analogues **2b** (41%) and **2c** (37%) were prepared by condensation of the aldehyde **3** with bis-Wittig salts **25**[15a] -and **26**. The analogue **2d** was prepared (42%) by Wittig reaction between the phosphonium salt **4b** and the dialdehyde **27**, which was obtained from the acetal-aldehyde **28**[16] as shown in Scheme 4. These analogues **2a**–**d** were all produced in a stereoselective manner.

Singlet-oxygen-quenching activities of astaxanthin analogues 2a–d

Finally, singlet-oxygen-quenching activities of astaxanthin analogues **2a**–**d** (Fig. 1) having polyene chains of various

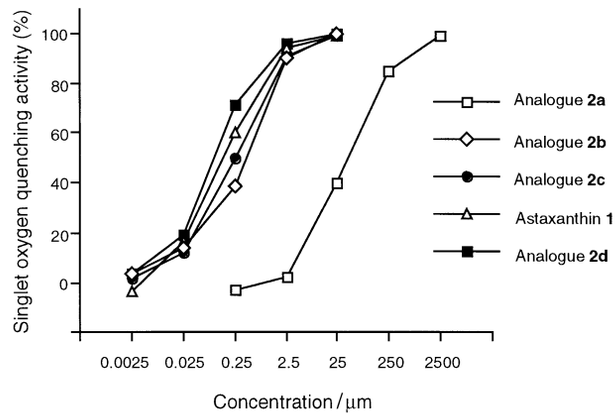
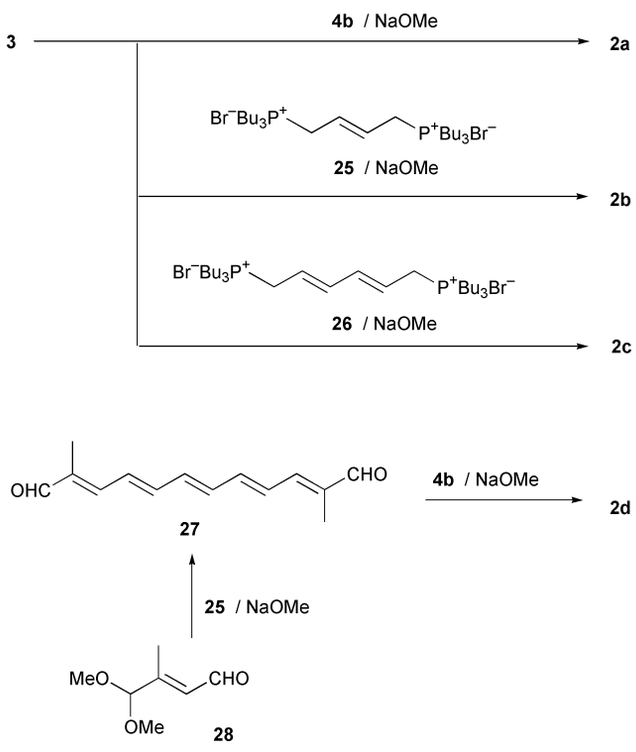


Fig. 2 Singlet oxygen quenching activites of astaxanthin **1** and its analogues **2a**–**d**.



Scheme 4

lengths were examined according to the method using a thermodissociable endoperoxide[17] of 1,4-dimethylnaphthalene as a singlet-oxygen-generator[3d] and 2,2,6,6-tetramethylpiperidine (TEMP), a spin-trap agent, as a detector[18] of singlet oxygen.

Results are shown in Fig. 2. Analogues **2b**–**d** showed strong quenching activities in agreement with astaxanthin **1**; however, analogue **2a**, having the shortest polyene chain, revealed low activity. It is found that the ability of astaxanthin analogues to quench singlet oxygen is strongly affected by the length of conjugated polyene chain.

Studies on the antioxidation mechanism of 3-hydroxy-4-oxo-β-end-groups conjugated to the polyene chain in astaxanthin are now in progress.

Experimental

Mps were measured on a micro melting-point apparatus (Yanagimoto) and are uncorrected. UV–visible spectra were recorded on a JASCO Ubest-55 instrument for ethanol solutions. IR spectra were measured on a Perkin-Elmer FT-IR spectrometer, model Paragon 1000, for chloroform solutions. ^1H NMR spectra at 300 or 500 MHz and ^{13}C NMR spectra at 75 or

125 MHz were determined on a Varian Gemini-300 or a Varian VXR-500 superconducting FT-NMR spectrometer, respectively, for deuteriochloroform solutions (tetramethylsilane as internal reference). *J*-Values are given in Hz. Mass spectra were taken on a Hitachi M-4100 spectrometer. Optical rotations were measured on a JASCO DIP-181 polarimeter ($[\alpha]_D$-values are in units of 10^{-1} deg cm^2 g^{-1}). EPR spectra were recorded on a JEOL JES-FR30 spectrometer using the signal given by paramagnetic resonance of Mn^{2+} as an internal standard.

Column chromatography (CC) was performed on silica gel (Merck Art. 7734). Short-column chromatography (SCC) was conducted on silica gel (Merck Art. 7739) under reduced pressure. Preparative HPLC was carried out on a Waters Model 510 instrument with a UV–visible detector.

All operations were carried out under nitrogen or argon. Ether refers to diethyl ether except where specified otherwise, and hexane to *n*-hexane. NMR assignments are given using the carotenoid numbering system. Extracts were dried over anhydrous Na_2SO_4.

(7a*S*)-5-Ethynyl-5,6,7,7a-tetrahydro-2,2,4,6,6-pentamethylbenzo-1,3-dioxol-5-ol 6

A solution of BuLi (1.50 M in hexane; 21.4 cm^3, 32 mmol) was added to a solution of TMS-acetylene (3.15 g, 32 mmol) in dry THF (30 cm^3) at 0 °C and the mixture was stirred for a further 30 min. To this mixture was added dropwise a solution of the ketone **5**[5] (4.50 g, 21 mmol) in dry THF (30 cm^3) at 0 °C and the mixture was stirred at room temperature for 2 h. After being quenched with saturated aq. NH_4Cl, the mixture was extracted with ether. The extracts were washed with brine, dried and evaporated to give a residue which, without purification, was dissolved in methanol (30 cm^3). Aq. 10% KOH was added to this solution at 0 °C and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with ether and washed with brine. Evaporation of the dried solution gave a residue, which was purified by SCC (ether–hexane, 1 : 4) to afford the terminal alkyne **6** (4.97 g, 98% from **5**) as a colourless oil; $[\alpha]_D^{23}$ + 178.4 (*c* 0.97, EtOH); λ_{max}/nm 212; ν_{max}/cm^{-1} 3603 and 3482 (OH), 3305 (≡C-H), 2110 (C≡C), 1725 (C=C-O); δ_H(300 MHz) 1.08 and 1.22 (each 3H, s, 1-*gem*-CH_3), 1.47 and 1.48 [each 3H, s, $OC(CH_3)_2O$], 1.77 (3H, s, 5-CH_3), 1.81 (1H, dd, *J* 12 and 10, 2-H_{ax}), 1.91 (1H, dd, *J* 12 and 6, 2-H_{eq}), 2.50 (1H, s, C≡CH), 4.50 (1H, m, 3-H) (Found: M^+, 236.1422. $C_{14}H_{20}O_3$ requires *M*, 236.1411).

Radical hydrostannylation of terminal alkyne 6

A mixture of alkyne **6** (3.58 g, 15.2 mmol) and tri-*n*-butyltin hydride (6.62 g, 22.7 mmol) was heated at 120 °C for 2 h in the presence of a catalytic amount of AIBN (*ca.* 30 mg). The resulting crude product was purified by SCC (ether–hexane, 1 : 3) to give the *E*-vinylstannane **7a** (3.17 g, 40%) as a colourless oil and the *Z*-isomer **7b** (3.06 g, 38%) as a colourless solid.

Compound 7a. $[\alpha]_D^{25}$ −167.4 (*c* 0.93, MeOH); ν_{max}/cm^{-1} 3606 and 3499 (OH), 1722 (C=C-O), 1590 (C=C); δ_H(300 MHz) 0.84–0.92 (18H, m, 1-CH_3, $CH_2 \times 3$ and $CH_2CH_3 \times 3$), 1.10 (3H, s, 1-CH_3), 1.23–1.33 (6H, m, $CH_2 \times 3$), 1.42–1.56 (6H, m, $CH_2 \times 3$), 1.47 (3H, d, *J* 1.5, 5-CH_3), 1.48 and 1.50 [each 3H, s, $OC(CH_3)_2O$], 1.66 (1H, dd, *J* 12 and 10.5, 2-H_{ax}), 1.80 (1H, dd, *J* 12 and 6, 2-H_{eq}), 4.51 (1H, m, 3-H), 5.84 (1H, d, *J* 19, J^1H–^{117}Sn 63, J^1H–^{119}Sn 66, 7-H or 8-H), 5.99 (1H, d, *J* 19, J^1H–^{117}Sn 69, J^1H–^{119}Sn 72, 8-H or 7-H).

Compound 7b. $[\alpha]_D^{25}$ +216.5 (*c* 1.00, MeOH); ν_{max}/cm^{-1} 3616 and 3500 (OH), 1719 (C=C-O), 1594 (C=C); δ_H(300 MHz) 0.84–0.91 (18H, m, 1-CH_3, $CH_2 \times 3$ and $CH_2CH_3 \times 3$), 1.05 (3H, s, 1-CH_3), 1.25–1.37 (6H, m, $CH_2 \times 3$), 1.42–1.55 (6H, m, $CH_2 \times 3$), 1.47 and 1.48 [each 3H, s, $OC(CH_3)_2O$], 1.49 (3H, d, *J* 1.5, 5-CH_3), 1.73 (1H, dd, *J* 12 and 10.5, 2-H_{ax}), 1.88 (1H, dd, *J* 12 and 6, 2-H_{eq}), 4.50 (1H, m, 3-H), 5.93 (1H, d, *J* 13, J^1H–^{117}Sn 68, J^1H–^{119}Sn 72, 8-H), 6.27 (1H, dd-like, *J* 13 and 1.5, J^1H–^{117}Sn 139, J^1H–^{119}Sn 146, 7-H).

Palladium-catalyzed hydrostannylation of terminal alkyne 6

To a solution of alkyne **6** (506 mg, 2.14 mmol) in THF (6 cm^3) was added $PdCl_2(PPh_3)_2$ (30 mg, 0.04 mmol) followed by tri-*n*-butyltin hydride (750 mg, 2.58 mmol) over a period of *ca.* 1–2 min. After being stirred at room temperature for 10 min, the reaction mixture was concentrated *in vacuo*. The residue was purified by SCC (ether–hexane, 1 : 9) to give the *E*-vinylstannane **7a** (780 mg, 68%).

Isomerization of *Z*-vinylstannane 7b

A mixture of *Z*-vinylstannane **7b** (5.00 g, 9.49 mmol) and tri-*n*-butyltin hydride (8.28 g, 28.5 mmol) was heated at 120 °C for 1 h in the presence of a catalytic amount of AIBN (*ca.* 50 mg). The resulting crude product was purified by SCC (ether–hexane, 1 : 3) to give the *E*-vinylstannane **7a** (3.35 g, 67%) and the *Z*-isomer **7b** (1.10 g, 22% recovery).

(6*S*)-6-Hydroxy-2,4,4-trimethyl-3-[(*E*)-2-(tri-*n*-butylstannyl)-ethenyl]cyclohex-2-enone 8

Aq. H_2SO_4 (1.5 M; 50 cm^3) was added to a solution of the *E*-vinylstannane **7a** (5.04 g, 9.6 mmol) in THF (250 cm^3) at 0 °C. The mixture was stirred at room temperature for 30 min and neutralized with saturated aq. $NaHCO_3$. The organics were extracted with ether and washed with brine. Evaporation of the dried solution gave a residue, which was purified by CC (ether–hexane, 1 : 4) to provide the hydroxy ketone **8** (4.10 g, 92%) as a colourless oil; $[\alpha]_D^{25}$ −102.5 (*c* 1.06, MeOH); λ_{max}/nm 259; ν_{max}/cm^{-1} 3494 (OH), 1664 (conj. C=O), 1590 (C=C); δ_H(300 MHz) 0.87–0.99 (15H, m, $CH_2 \times 3$ and $CH_2CH_3 \times 3$), 1.15 and 1.29 (each 3H, s, 1-*gem*-CH_3), 1.25–1.39 (6H, m, $CH_2 \times 3$), 1.48–1.58 (6H, m, $CH_2 \times 3$), 1.80 (1H, t-like, *J* 14, 2-H_{ax}), 1.85 (3H, d, *J* 1, 5-CH_3), 2.15 (1H, dd, *J* 12 and 5.5, 2-H_{eq}), 3.68 (1H, s, OH), 4.32 (1H, dd, *J* 14 and 5.5, 3-H), 6.22 (1H, d, *J* 20, J^1H–^{117}Sn 69, J^1H–^{119}Sn 72, 8-H), 6.46 (1H, dd-like, *J* 20 and 0.5, J^1H–^{117}Sn 62, J^1H–^{119}Sn 65, 7-H).

(6*S*)-6-Acetoxy-2,4,4-trimethyl-3-[(*E*)-2-(tri-*n*-butylstannyl)-ethenyl]cyclohex-2-enone 9

Ac_2O (4.5 cm^3) was added to a solution of the hydroxy ketone **8** (3.02 g, 6.5 mmol) in pyridine (Py) (16 cm^3) and the reaction mixture was stirred at room temperature for 2 h, poured into ice–water, and extracted with ether. The extracts were washed successively with aq. 5% HCl, saturated aq. $NaHCO_3$, and brine. Evaporation of the dried extracts gave a residue, which was purified by CC (ether–hexane, 1 : 3) to afford the acetate **9** (3.21 g, 97%) as a colourless oil; $[\alpha]_D^{25}$ −87.8 (*c* 1.11, MeOH); λ_{max}/nm 265; ν_{max}/cm^{-1} 1742 (OAc), 1680 (conj. C=O), 1596 (C=C); δ_H(300 MHz) 0.87–1.00 (15H, m, $CH_2 \times 3$ and $CH_2CH_3 \times 3$), 1.17 and 1.32 (each 3H, s, 1-*gem*-CH_3), 1.27–1.39 (6H, m, $CH_2 \times 3$), 1.48–1.60 (6H, m, $CH_2 \times 3$), 1.81 (3H, d, *J* 1, 5-CH_3), 2.00 (1H, dd, *J* 13 and 6.5, 2-H_{eq}), 2.10 (1H, t, *J* 13, 2-H_{ax}), 2.18 (3H, s, OAc), 5.51 (1H, dd, *J* 13 and 6.5, 3-H), 6.20 (1H, d, *J* 20, J^1H–^{117}Sn 69, J^1H–^{119}Sn 72, 8-H), 6.46 (1H, dd-like, *J* 20 and 1, J^1H–^{117}Sn = J^1H–^{119}Sn ≈ 63, 7-H).

Coupling reaction of the vinylstannane 9 with the vinyl bromide 10 (Table 1); representative procedure (Run 6)

To a degassed solution of the vinylstannane **9** (217 mg, 0.42 mmol) and the vinyl bromide **10** (128 mg, 0.85 mmol) in DMF (6 cm^3) were added Pd_2dba_3 (11 mg, 0.012 mmol) and $AsPh_3$ (31 mg, 0.10 mmol) and the mixture was stirred at 50 °C for 24 h. After being quenched by addition of aq. 10% NH_4OH, the mixture was extracted with ether. The extracts were washed

with brine, dried and evaporated to give a residue, which was purified by SCC (acetone–ether–hexane, 3 : 10 : 20) to give the alcohol **11** (68 mg, 55%) and the dimer **12** (16 mg, 17%).

Compound 11. $[\alpha]_D^{27}$ −156.6 (*c* 0.97, MeOH); λ_{max}/nm 231, 301; ν_{max}/cm^{-1} 3610 and 3468 (OH), 1740 (OAc), 1679 (conj. C=O), 1612 and 1587 (C=C); δ_H(300 MHz) 1.18 and 1.32 (each 3H, s, 1-*gem*-CH_3), 1.84 and 1.86 (each 3H, s, 5-CH_3 and 9-CH_3), 1.99 (1H, dd, *J* 12.5 and 6.5, 2-H_{eq}), 2.06 (1H, t, *J* 12.5, 2-H_{ax}), 2.17 (3H, s, OAc), 4.33 (2H, d, *J* 6.5, 11-H_2), 5.51 (1H, dd, *J* 12.5 and 6.5, 3-H), 5.76 (1H, br t, *J* 6.5, 10-H), 6.15 (1H, br d, *J* 16, 7-H), 6.26 (1H, d, *J* 16, 8-H) (Found: M$^+$, 292.1653. $C_{17}H_{24}O_4$ requires *M*, 292.1673).

Compound 12. λ_{max}/nm 225, 328; ν_{max}/cm^{-1} 1739 (OAc), 1681 (conj. C=O), 1588 (C=C); δ_H(300 MHz) 1.22 and 1.35 (each 6H, s, 1-*gem*-CH_3 and 1′-*gem*-CH_3), 1.90 (6H, s, 5-CH_3 and 5′-CH_3), 2.01 (2H, dd, *J* 13 and 6.5, 2′-H_{ax} and 2-H_{ax}), 2.07 (2H, t, *J* 13, 2′-H_{eq} and 2-H_{eq}), 2.18 (6H, s, OAc × 2), 5.51 (2H, dd, *J* 13 and 6.5, 3-H and 3′-H), 6.28–6.43 (4H, m, 7-H, 7′-H, 8-H and 8′-H) (Found: M$^+$, 442.2354. $C_{26}H_{34}O_6$ requires *M*, 442.2353).

(2*E*,4*E*)-5-[(4*S*)-4-Acetoxy-2,6,6-trimethyl-3-oxocyclohex-1-enyl]-3-methylpenta-2,4-dienal 13

The alcohol **11** (532 mg, 1.82 mmol) was dissolved in ether–hexane (1 : 2) and shaken with active MnO_2 (2.7 g) at room temperature for 1 h. The mixture was filtered through Celite. Evaporation of the filtrate gave a residue, which was purified by SCC (acetone–hexane, 1 : 3) to afford the aldehyde **13** (383 mg, 72%) as a pale yellow oil; $[\alpha]_D^{23}$ −134.2 (*c* 1.03, EtOH); λ_{max}/nm 250, 300; ν_{max}/cm^{-1} 1740 (OAc), 1665 (conj. C=O and conj. CHO), 1616 and 1596 (C=C); δ_H(300 MHz) 1.21 and 1.37 (each 3H, s, 1-*gem*-CH_3), 1.85 (3H, s, 5-CH_3), 2.04 (1H, dd, *J* 13 and 6.5, 2-H_{eq}), 2.11 (1H, t, *J* 13, 2-H_{ax}), 2.19 (3H, s, OAc), 2.35 (3H, s, 9-CH_3), 5.53 (1H, dd, *J* 13 and 6.5, 3-H), 6.02 (1H, br d, *J* 8, 10-H), 6.35 (1H, d, *J* 16, 8-H), 6.70 (1H, br d, *J* 16, 7-H), 10.16 (1H, d, *J* 8, CHO) (Found: M$^+$, 290.1543. $C_{17}H_{22}O_4$ requires *M*, 290.1516).

(2*E*,4*E*)-5-[(4*S*)-4-Hydroxy-2,6,6-trimethyl-3-oxocyclohex-1-enyl]-3-methylpenta-2,4-dienal 3

NaOMe (1.0 M in MeOH; 0.5 cm^3, 0.5 mmol) was added to a solution of the acetate **13** (204 mg, 0.70 mmol) in MeOH (10 cm^3) and the mixture was stirred at room temperature for 15 min. To this reaction mixture was added Dowex 50W-X8 (H^+) (500 mg) and the mixture was stirred at room temperature for 10 min. After the Dowex had been filtered off, the filtrate was evaporated. The residue was purified by SCC (acetone–hexane, 3 : 7) to give the alcohol **3** (141 mg, 81%) as a pale yellow oil; $[\alpha]_D^{26}$ −94.1 (*c* 1.01, EtOH); λ_{max}/nm 251, 301; ν_{max}/cm^{-1} 3495 (OH), 1666 (conj. C=O and conj. CHO), 1616 and 1596 (C=C); δ_H(300 MHz) 1.15 and 1.30 (each 3H, s, 1-*gem*-CH_3), 1.81 (1H, t, *J* 13, 2-H_{ax}), 1.85 (3H, s, 5-CH_3), 2.15 (1H, dd, *J* 13 and 6, 2-H_{eq}), 2.31 (3H, s, 9-CH_3), 3.61 (1H, br s, OH), 4.32 (1H, ddd, *J* 13, 6 and 2, 3-H), 5.98 (1H, br d, *J* 8, 10-H), 6.32 (1H, d, *J* 16.5, 8-H), 6.67 (1H, br d, *J* 16.5, 7-H), 10.13 (1H, d, *J* 8, CHO) (Found: M$^+$, 248.1433. $C_{15}H_{20}O_3$ requires *M*, 248.1412).

(6*S*)-6-Hydroxy-3-[(1*E*,3*E*)-5-hydroxy-3-methylpenta-1,3-dienyl]-2,4,4-trimethylcyclohex-2-enone 14

According to the procedure described in the preparation of the alcohol **3**, methanolysis of the acetate **11** (334 mg) followed by purification using SCC (ether–hexane, 4 : 1) gave the diol **14** (164 mg, 57%) as a pale yellow oil; $[\alpha]_D^{25}$ −157.6 (*c* 1.03, EtOH); λ_{max}/nm 229, 298; ν_{max}/cm^{-1} 3611 and 3489 (OH), 1664 (conj. C=O), 1610 and 1595 (C=C); δ_H(300 MHz) 1.17 and 1.30 (each 3H, s, 1-*gem*-CH_3), 1.81 (1H, t, *J* 13, 2-H_{ax}), 1.87 and 1.89 (each 3H, s, 5-CH_3 and 9-CH_3), 2.15 (1H, dd, *J* 13 and 5.5, 2-H_{eq}), 3.70 (1H, br s, OH), 4.32 (1H, m, 3-H), 4.35 (2H, d, *J* 6.5, 11-H_2), 5.78 (1H, br t, *J* 6.5, 10-H), 6.17 (1H, br d, *J* 16.5, 7-H), 6.27 (1H, d, *J* 16.5, 8-H) (Found: M$^+$, 250.1592. $C_{15}H_{22}O_3$ requires *M*, 250.1578).

Tri-*n*-butyl{(2*E*,4*E*)-5-[(4*S*)-4-hydroxy-2,6,6-trimethyl-3-oxocyclohex-1-enyl]-3-methylpenta-2,4-dienyl}phosphonium bromide 4b

According to the literature procedure,[11] aq. 48% HBr (10.6 cm^3, 5.1 mmol) was added dropwise to an ice-cooled solution of the alcohol **14** (1.00 g, 4.0 mmol) in CH_2Cl_2 (10 cm^3) and the mixture was stirred for further 5 min. After addition of a small amount of 1,2-epoxybutane, the mixture was poured into saturated aq. $NaHCO_3$ and extracted with ether. The extracts were washed with brine, dried, and evaporated to give the bromide which, without purification, was dissolved in ether (15 cm^3) and PBu_3 (1.2 cm^3, 0.48 mmol) was added to it. After being stirred at room temperature for 1 h, the resulting precipitate was filtered off, and washed with ether to provide the phosphonium salt **4b** (1.59 g, 77% from **14**); δ_H(300 MHz) 0.92 (9H, t, *J* 7, CH_3 × 3) 1.12 and 1.26 (each 3H, s, 1-*gem*-CH_3), 1.49 [12H, m, (CH_2CH_2) × 3], 1.76 (1H, t, *J* 13, 2-H_{ax}), 1.83 (3H, s, 5-CH_3), 1.99 (3H, br d, *J* 3.5, 9-CH_3), 2.12 (1H, dd, *J* 13 and 6, 2-H_{eq}), 2.43 (6H, m, PCH_2 × 3), 3.74 (2H, dd, *J* 16.5 and 7.5, 11-H_2), 4.28 (1H, dd, *J* 13 and 6, 3-H), 5.47 (1H, br q, *J* 7.5, 10-H), 6.18 (1H, br d, *J* 16.5, 7-H), 6.25 (1H, d, *J* 16.5, 8-H).

(6*S*)-3-Ethynyl-6-hydroxy-2,4,4-trimethylcyclohex-2-enone 15

In the same manner as described for the preparation of the ketone **8**, acid hydrolysis of compound **6** (988 mg) followed by purification by SCC (acetone–hexane, 1 : 6) provided the ketone **15** (624 mg, 84%) as a colourless oil; $[\alpha]_D^{23}$ −195.1 (*c* 1.02, EtOH); λ_{max}/nm 266; ν_{max}/cm^{-1} 3505 (OH), 3301 (≡C-H), 2092 (C≡C), 1672 (conj. C=O), 1586 (C=C); δ_H(300 MHz) 1.29 and 1.34 (each 3H, s, 1-*gem*-CH_3), 1.78 (1H, t, *J* 13, 2-H_{ax}), 2.01 (3H, s, 5-CH_3), 2.21 (1H, dd, *J* 13 and 5.5, 2-H_{eq}), 3.55 (1H, d, *J* 2, OH), 3.79 (1H, s, C≡CH), 4.33 (1H, ddd, *J* 13, 5.5 and 2, 3-H) (Found: M$^+$, 178.1002. $C_{11}H_{14}O_2$ requires *M*, 178.0993).

(6*S*)-6-Acetoxy-3-ethynyl-2,4,4-trimethylcyclohex-2-enone 16

According to the procedure described in the preparation of the acetate **9**, acetylation of the alcohol **15** (2.40 g) followed by purification by CC (acetone–hexane, 1 : 5) afforded the acetate **16** (2.74 g, 93%) as a colourless oil; $[\alpha]_D^{23}$ −166.0 (*c* 1.03, EtOH); λ_{max}/nm 267; ν_{max}/cm^{-1} 3544 (OH), 3301 (≡C-H), 2092 (C≡C), 1743 (OAc), 1690 (conj. C=O), 1587 (C=C); δ_H(300 MHz) 1.30 and 1.36 (each 3H, s, 1-*gem*-CH_3), 1.97 (3H, s, 5-CH_3), 2.03 (2H, m, 2-H_2), 2.16 (3H, s, OAc), 3.79 (1H, s, C≡CH), 5.49 (1H, dd, *J* 12.5 and 7, 3-H) (Found: M$^+$, 220.1085. $C_{13}H_{16}O_3$ requires *M*, 220.1099).

Coupling reaction of terminal alkyne 15 with the vinyl bromide 10 (Table 2); representative procedure (Run 4)

To a stirred, degassed mixture of the vinyl bromide **10** (986 mg, 6.75 mmol), $Pd(PPh_3)_4$ (226 mg, 0.20 mmol), Et_2NH (1.05 cm^3, 10.1 mmol), CuI (200 mg, 1.05 mmol) and BHT (48 mg, 0.22 mmol) in dry benzene (20 cm^3) was added dropwise a degassed solution of alkyne **15** (775 mg, 4.35 mmol) in dry benzene (10 cm^3) over a period of 2 h by use of a syringe pump. After being stirred at room temperature for a further 30 min, the mixture was diluted with ether and the organic layer was washed successively with aq. 3% HCl, saturated aq. $NaHCO_3$, and brine. Evaporation of the dried solvent gave a residue, which was purified by SCC (acetone–hexane, 1 : 3) to give the alcohol **17** (828 mg, 76%) and the dimer **18** (184 mg, 24%).

Compound 17. Mp 86–88 °C (from hexane–diisopropyl ether) (lit.[11], 90–92 °C); $[\alpha]_D^{23}$ −199.23 (*c* 0.99, EtOH) {lit.,[11] $[\alpha]_D^{20}$

−202.6 (*c* 1.0, EtOH)}; λ_{max}/nm 306; ν_{max}/cm^{-1} 3610 and 3494 (OH), 2183 (C≡C), 1665 (conj. C=O), 1576 (C=C); δ_H(300 MHz) 1.29 and 1.34 (each 3H, s, 1-*gem*-CH_3), 1.79 (1H, t, *J* 13, 2-H_{ax}), 1.92 (3H, s, 9-CH_3), 2.00 (3H, s, 5-CH_3), 2.21 (1H, dd, *J* 13 and 5.5, 2-H_{eq}), 3.59 (1H, d, *J* 1.5, OH), 4.33 (3H, m, 3-H and 11-H_2), 6.14 (1H, tq, *J* 7 and 1.5, 10-H) (Found: M$^+$, 248.1430. $C_{15}H_{20}O_3$ requires *M*, 248.1411).

Compound 18. Mp 180–183 °C (from hexane–ether); $[\alpha]_D^{23}$ −326.7 (*c* 0.99, EtOH); λ_{max}/nm 228, 265 (sh), 279, 290, 314, 334, 358; ν_{max}/cm^{-1} 3499 (OH), 2127 (C≡C), 1664 (conj. C=O), 1629 and 1575 (C=C); δ_H(300 MHz) 1.29 and 1.34 (each 6H, s, 1-*gem*-CH_3 and 1′-*gem*-CH_3), 1.82 (2H, t, *J* 13, 2′-H_{ax} and 2-H_{ax}), 2.06 (6H, s, 5′-CH_3 and 5-CH_3), 2.23 (2H, dd, *J* 13 and 6, 2′-H_{eq} and 2-H_{eq}), 3.54 (2H, br s, OH × 2), 4.36 (2H, dd, *J* 13 and 6, 3-H and 3′-H) (Found: C, 74.27; H, 7.45; M$^+$, 354.1828. $C_{22}H_{26}O_4$ requires C, 74.55; H, 7.39%; *M*, 354.1829).

(6*S*)-6-Acetoxy-3-[(3*E*)-5-hydroxy-3-methylpent-3-en-1-ynyl]-2,4,4-trimethylcyclohex-2-enone 19

The coupling reaction of the alkyne **16** (778 mg, 3.53 mmol) with the vinyl bromide **10** (871 mg, 5.77 mmol) was carried out in the same manner as above. The resulting crude product was purified by SCC (acetone–hexane, 1 : 3) to give the alcohol **19** (978 mg, 95%) as a pale yellow oil; $[\alpha]_D^{23}$ −183.3 (*c* 1.02, EtOH); λ_{max}/nm 310; ν_{max}/cm^{-1} 3609 and 3480 (OH), 2182 (C≡C), 1740 (OAc), 1681 (conj. C=O), 1578 (C=C); δ_H(300 MHz) 1.30 and 1.37 (each 3H, s, 1-*gem*-CH_3), 1.92 (3H, s, 9-CH_3), 1.97 (3H, s, 5-CH_3), 2.05 (2H, m, 2-H_2), 2.18 (3H, s, OAc), 4.31 (2H, br t, *J* 6, 11-H_2), 5.51 (1H, dd, *J* 12 and 7.5, 3-H), 6.14 (1H, tq, *J* 6 and 1.5, 10-H) (Found: M$^+$, 290.1538. $C_{17}H_{22}O_4$ requires *M*, 290.1516).

(7a*S*)-5-[(3*E*)-5-Hydroxy-3-methylpent-3-en-1-ynyl]-5,6,7,7a-tetrahydro-2,2,4,6,6-pentamethylbenzo-1,3-dioxol-5-ol 20

According to the procedure described in the preparation of the alcohol **17**, the coupling reaction of the alkyne **6** (3.57 g, 15.1 mmol) with the vinyl bromide **10** (3.57 g, 23.6 mmol) followed by purification using SCC (acetone–hexane, 1 : 3) provided the alcohol **20** (5.21 g, 86%) as a pale yellow oil; $[\alpha]_D^{23}$ + 229.2 (*c* 0.96, EtOH); ν_{max}/cm^{-1} 3610 and 3480 (OH), 2184 (C≡C), 1724 (C=C-O), 1663 and 1633 (C=C); δ_H(300 MHz) 1.09 and 1.21 (each 3H, s, 1-*gem*-CH_3), 1.48 and 1.50 [each 3H, s, $OC(CH_3)_2O$], 1.77 (3H, s, 5-CH_3), 1.81 (3H, s, 9-CH_3), 1.92 (2H, m, 2-H_2), 4.22 (2H, br t, *J* 6, 11-H_2), 4.52 (1H, m, 3-H), 5.96 (1H, tq, *J* 6 and 1.5, 10-H) (Found: M$^+$, 306.1823. $C_{18}H_{26}O_4$ requires *M*, 306.1830).

Preparation of C_{15}-aldehyde 3 from α-acetylenic alcohol 20

A solution of α-acetylenic alcohol **20** (1.63 g, 5.33 mmol) in THF (20 cm^3) was added dropwise to a stirred suspension of $LiAlH_4$ (504 mg, 13.3 mmol) and NaOMe (57 mg, 1.06 mmol) in THF (50 cm^3) at 0 °C and the mixture was stirred at 0 °C for 10 min and at room temperature for 1 h. The excess of $LiAlH_4$ was decomposed by dropwise additon of water. After evaporation of THF, the residue was extracted with ether. The extracts were washed with brine, dried, and evaporated to afford a crude alcohol **21**, which without purification was dissolved in ether–hexane (1 : 3) and shaken with active MnO_2 (9 g) at room temperature for 3 h. The mixture was filtered through Celite. Evaporation of the filtrate gave a residue, which without purification was treated with acid according to the preparation of the ketone **8**. The resulting crude product was purified by SCC (acetone–hexane, 1 : 2) to afford the aldehyde **3** (1.09 g, 83% from **20**). Spectral properties of this aldehyde **3** were in agreement with those obtained by alcoholysis of the acetate **13**.

Preparation of C_{15}-alcohol 14 from α-acetylenic alcohol 20

Reduction of the α-acetylenic alcohol **20** (1.00 g) was carried out in the same manner as above to afford the crude alcohol **21**, which without purification, was treated with acid according to the procedure described in the preparation of the ketone **8**. The resulting crude product was purified by SCC (acetone–hexane, 3 : 7) to afford the diol **14** (560 mg, 65% from **20**). Spectral properties of this diol **14** were in agreement with those obtained by alcoholysis of the acetate **11**.

(6*S*)-3-[(1*E*,3*E*,5*E*)-3,8-Dimethylnona-1,3,5,7-tetraenyl]-6-hydroxy-2,4,4-trimethylcyclohex-2-enone 23a

A solution of NaOMe (1.0 M in MeOH; 2.98 cm^3, 2.98 mmol) was added to an ice-cooled solution of the Wittig salt **4b** (1.44 g, 2.98 mmol) and the aldehyde **22** (100 mg, 1.19 mmol) in CH_2Cl_2 (20 cm^3). After being stirred at room temperature for 40 min, the reaction mixture was diluted with ether. The organic layer was washed with brine, dried, and evaporated to give a residue, which was purified by SCC (ether–hexane, 1 : 2) to afford the all-*E* pentaenone **23a** (260 mg, 73%) as a yellow oil; λ_{max}/nm 280, 362; ν_{max}/cm^{-1} 3490 (OH), 1659 (conj. C=O), 1610 and 1566 (C=C); δ_H(300 MHz) 1.20, 1.31 (each 3H, s, 1-*gem*-CH_3), 1.80 (1H, m, 2-H_{ax}), 1.81 and 1.84 (each 3H, s, 14-*gem*-CH_3), 1.93 and 1.94 (each 3H, s, 5-CH_3 and 9-CH_3), 2.15 (1H, dd, *J* 12.5 and 5.5, 2-H_{eq}), 3.71 (1H, d, *J* 2, OH), 4.32 (1H, ddd, *J* 13.5, 5.5 and 2, 3-H), 5.98 (1H, dm, *J* 10.5, 13-H), 6.16 (1H, br d, *J* 16, 7-H), 6.26 (1H, br d, *J* 11, 10-H), 6.40 (1H, d, *J* 16, 8-H), 6.46 (1H, dd, *J* 14.5 and 11, 11-H), 6.56 (1H, dd, *J* 14.5 and 10.5, 12-H) (Found: M$^+$, 300.2090. $C_{20}H_{28}O_2$ requires *M*, 300.2088).

(6*S*)-6-Acetoxy-3-[(1*E*,3*E*,5*E*/*Z*)-3,8-dimethylnona-1,3,5,7-tetraenyl]-2,4,4-trimethylcyclohex-2-enone 24a,b

In the same manner as described above, Wittig reaction of the phosphonium salt **4a** [11] (2.05 g, 3.56 mmol) with the aldehyde **22** (100 mg, 1.19 mmol) followed by purification by SCC (ether–hexane, 1 : 2) provided an isomeric mixture of compound **23** (304 mg, 85%), which without separation was acetylated in the same manner as described for the preparation of the acetate **9**. The resulting crude products were purified by SCC (acetone–hexane, 1 : 3) to provide the all-*E*-pentaenone **24a** (90 mg, 22%) and the 11*Z*-isomer **24b** (90 mg, 22%) each as a yellow oil.

Compound 24a. λ_{max}/nm 282, 363; ν_{max}/cm^{-1} 1740 (OAc), 1675 (conj. C=O), 1568 (C=C); δ_H(300 MHz) 1.22 and 1.34 (each 3H, s, 1-*gem*-CH_3), 1.81 and 1.84 (each 3H, s, 14-*gem*-CH_3), 1.89 (3H, s, 5-CH_3), 1.94 (3H, s, 9-CH_3), 2.00 (1H, dd, *J* 12.5 and 6.5, 2-H_{eq}), 2.07 (1H, t, *J* 12.5, 2-H_{ax}), 2.19 (3H, s, OAc), 5.52 (1H, dd, *J* 12.5 and 6.5, 3-H), 5.98 (1H, dm, *J* 10.5, 13-H), 6.15 (1H, br d, *J* 16, 7-H), 6.25 (1H, br d, *J* 11, 10-H), 6.37 (1H, d, *J* 16, 8-H), 6.45 (1H, dd, *J* 14.5 and 11, 11-H), 6.56 (1H, dd, *J* 14.5 and 10.5, 12-H) (Found: M$^+$, 342.2185. $C_{22}H_{30}O_3$ requires *M*, 342.2194).

Compound 24b. λ_{max}/nm 281, 361; ν_{max}/cm^{-1} 1740 (OAc), 1675 (conj. C=O), 1607 and 1571 (C=C); δ_H(300 MHz) 1.22 and 1.35 (each 3H, s, 1-*gem*-CH_3), 1.81 and 1.88 (each 3H, s, 14-*gem*-CH_3), 1.90 (3H, s, 5-CH_3), 1.95 (3H, s, 9-CH_3), 2.01 (1H, dd, *J* 12.5 and 6.5, 2-H_{eq}), 2.07 (1H, t, *J* 12.5, 2-H_{ax}), 2.19 (3H, s, OAc), 5.53 (1H, dd, *J* 12.5 and 6.5, 3-H), 6.19 (1H, br d, *J* 16, 7-H), 6.19–6.37 (3H, m, 11-H, 12-H and 13-H), 6.43 (1H, d, *J* 16, 8-H), 6.64 (1H, br d, *J* 11.5, 10-H) (Found: M$^+$, 342.2187. $C_{22}H_{30}O_3$ requires *M*, 342.2194).

(2*E*,4*E*,6*E*,8*E*,10*E*)-2,11-Dimethyldodeca-2,4,6,8,10-pentaenedial 27

A solution of NaOMe (1.0 M in MeOH; 2.5 cm^3, 2.5 mmol) was added to an ice-cooled solution of the diphosphonium salt

25[15a] (488 mg, 1.04 mmol) and the aldehyde **28**[16] (300 mg, 2.08 mmol) in CH_2Cl_2 (10 cm^3). After being stirred at room temperature for 1 h, the reaction mixture was diluted with ether. The organic layer was sufficiently shaken with aq. 5% HCl and then washed successively with saturated aq. $NaHCO_3$ and brine. Evaporation of the dried solution provided a residue, which was purifed by CC (ether–hexane–CH_2Cl_2, 1 : 4 : 4) to afford the dial **27** (121 mg, 54%) as a red solid; λ_{max}/nm 365 (sh), 385, 404; ν_{max}/cm^{-1} 1663 (conj. CHO), 1610 (C=C); δ_H(300 MHz) 1.90 (6H, s, 2-CH_3 and 11-CH_3), 6.60 (2H, m) and 6.68–6.84 (4H, m) (4-H, 5-H, 6-H, 7-H, 8-H and 9-H), 6.91 (2H, br d, *J* 10, 3-H and 10-H), 9.48 (2H, s, CHO × 2) (Found: M^+, 216.1161. $C_{14}H_{16}O_2$ requires *M*, 216.1150).

3,3′-[(1*E*,3*E*,5*E*,7*E*,9*E*)-3,8-Dimethyldeca-1,3,5,7,9-pentaene-1,10-diyl]bis[(6*S*)-6-hydroxy-2,4,4-trimethylcyclohex-2-enone] 2a

According to the procedure described in the preparation of the pentaenone **23a**, Wittig reaction of phosphonium salt **4b** (488 mg, 1.01 mmol) with the aldehyde **3** (100 mg, 0.40 mmol) and purification of the crude product by CC (EtOAc–benzene, 1 : 4) gave the analogue **2a** (131 mg, 70%) as a yellow oil; λ_{max}/nm 404; ν_{max}/cm^{-1} 3494 (OH), 1661 (conj. C=O), 1601 and 1573 (C=C); δ_H(500 MHz) 1.21 and 1.32 (each 6H, s, 1-*gem*-CH_3 and 1′-*gem*-CH_3), 1.82 (2H, t, *J* 13, 2-H_{ax} and 2′-H_{ax}), 1.94 (6H, s, 5-CH_3 and 5′-CH_3), 1.99 (6H, s, 9-CH_3 and 9′-CH_3), 2.16 (2H, dd, *J* 13 and 6, 2-H_{eq} and 2′-H_{eq}), 3.68 (2H, d, *J* 1.5, OH × 2), 4.33 (2H, ddd, *J* 13, 6 and 1.5, 3-H and 3′-H), 6.24 (2H, br d, *J* 16, 7-H and 7′-H), 6.32 (2H, br d, *J* 11, 10-H and 10′-H), 6.41 (2H, d, *J* 16, 8-H and 8′-H), 6.71 (2H, m, 11-H and 11′-H); δ_C(75 MHz) 12.55 (9-CH_3 and 9′-CH_3), 14.00 (5-CH_3 and 5′-CH_3), 26.14 and 30.72 (1-*gem*-CH_3 and 1′-*gem*-CH_3), 36.82 (C-1 and C-1′), 45.41 (C-2 and C-2′), 69.25 (C-3 and C-3′), 124.16 (C-7 and C-7′), 127.03 (C-5 and C-5′), 130.98 (C-11 and C-11′), 134.53 (C-10 and C-10′), 135.83 (C-9 and C-9′), 141.98 (C-8 and C-8′), 162.09 (C-6 and C-6′), 200.48 (C-4 and C-4′) (Found: M^+, 464.2938. $C_{30}H_{40}O_4$ requires *M*, 464.2924).

3,3′-[(1*E*,3*E*,5*E*,7*E*,9*E*,11*E*,13*E*)-3,12-Dimethyltetradeca-1,3,5,7,9,11,13-heptaene-1,14-diyl]bis[(6*S*)-6-hydroxy-2,4,4-trimethylcyclohex-2-enone] 2b

According to the procedure described in the preparation of the pentaenone **23a**, Wittig reaction of diphosphonium salt **25**[15a] (106 mg, 0.23 mmol) with the aldehyde **3** (112 mg, 0.45 mmol) and purification of the crude product by CC (EtOAc–benzene, 1 : 4) provided the analogue **2b** (48 mg, 41%) as a yellow solid; λ_{max}/nm 438; ν_{max}/cm^{-1} 3502 (OH), 1660 (conj. C=O), 1613 and 1569 (C=C); δ_H(500 MHz) 1.21 and 1.32 (each 6H, s, 1-*gem*-CH_3 and 1′-*gem*-CH_3), 1.81 (2H, t, *J* 13.5, 2-H_{ax} and 2′-H_{ax}), 1.94 (6H, s, 5-CH_3 and 5′-CH_3), 1.98 (6H, s, 9-CH_3 and 9′-CH_3), 2.16 (2H, dd, *J* 13 and 6, 2-H_{eq} and 2′-H_{eq}), 3.68 (2H, d, *J* 1.5, OH × 2), 4.32 (2H, ddd, *J* 13.5, 6 and 1.5, 3-H and 3′-H), 6.23 (2H, d, *J* 16, 7-H and 7′-H), 6.26 (2H, d, *J* 12, 10-H and 10′-H), 6.41 (2H, d, *J* 16, 8-H and 8′-H), 6.38–6.46 (4H, m, 12-H, 12′-H, 13-H and 13′-H), 6.66 (2H, m, 11-H and 11′-H); δ_C(125 MHz) 12.52 (9-CH_3 and 9′-CH_3), 13.99 (5-CH_3 and 5′-CH_3), 26.15 and 30.73 (1-*gem*-CH_3 and 1′-*gem*-CH_3), 36.81 (C-1 and C-1′), 45.42 (C-2 and C-2′), 69.22 (C-3 and C-3′), 123.85 (C-7 and C-7′), 126.95 (C-5 and C-5′), 129.76 (C-11 and C-11′), 134.36 and 134.54 (C-12, C-12′, C-13 and C-13′), 135.27 (C-10 and C-10′), 135.38 (C-9 and C-9′), 142.08 (C-8 and C-8′), 162.14 (C-6 and C-6′), 200.44 (C-4 and C-4′) (Found: M^+, 516.3247. $C_{34}H_{44}O_4$ requires *M*, 516.3236).

3,3′-[(1*E*,3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*E*)-3,14-Dimethylhexadeca-1,3,5,7,9,11,13,15-octaene-1,16-diyl]bis[(6*S*)-6-hydroxy-2,4,4-trimethylcyclohex-2-enone] 2c

According to the procedure described in the preparation of the pentaenone **23a**, Wittig reaction of diphosphonium salt **26**[15a] (100 mg, 0.20 mmol) with the aldehyde **3** (100 mg, 0.40 mmol) and purification of the crude product by CC (acetone–CH_2Cl_2, 5 : 95) provided the analogue **2c** (40 mg, 37%) as an orange solid; λ_{max}/nm 452; ν_{max}/cm^{-1} 3490 (OH), 1660 (conj. C=O), 1611 and 1562 (C=C); δ_H(500 MHz) 1.18 and 1.30 (each 6H, s, 1-*gem*-CH_3 and 1′-*gem*-CH_3), 1.79 (2H, t, *J* 13.5, 2-H_{ax} and 2′-H_{ax}), 1.92 (6H, s, 5-CH_3 and 5′-CH_3), 1.96 (6H, s, 9-CH_3 and 9′-CH_3), 2.13 (2H, dd, *J* 13 and 5.5, 2-H_{eq} and 2′-H_{eq}), 3.66 (2H, d, *J* 1.5, OH × 2), 4.30 (2H, ddd, *J* 13.5, 5.5 and 1.5, 3-H and 3′-H), 6.20 (2H, br d, *J* 16, 7-H and 7′-H), 6.23 (2H, br d, *J* 12.5, 10-H and 10′-H), 6.39 (8H, m, 8-H, 8′-H, 12-H, 12′-H, 13-H, 13′-H, 14-H and 14′-H), 6.61 (2H, m, 11-H and 11′-H); δ_C(75 MHz) 12.51 (9-CH_3 and 9′-CH_3), 13.98 (5-CH_3 and 5′-CH_3), 26.14 and 30.72 (1-*gem*-CH_3 and 1′-*gem*-CH_3), 36.79 (C-1 and C-1′), 45.40 (C-2 and C-2′), 69.22 (C-3 and C-3′), 123.77 (C-7 and C-7′), 126.92 (C-5 and C-5′), 129.57 (C-11 and C-11′), 134.12, 134.29 and 134.60 (C-12, C-12′, C-13, C-13′, C-14 and C-14′), 135.26 (C-9 and C-9′), 135.38 (C-10 and C-10′), 142.12 (C-8 and C-8′), 162.14 (C-6 and C-6′), 200.44 (C-4 and C-4′) (Found: M^+, 542.3393. $C_{36}H_{46}O_4$ requires *M*, 542.3394).

3,3′-[(1*E*,3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*E*,17*E*,19*E*,21*E*)-3,7,16,20-Tetramethyldocosa-1,3,5,7,9,11,13,15,17,19,21-undecaene-1,22-diyl]bis[(6*S*)-6-hydroxy-2,4,4-trimethylcyclohex-2-enone] 2d

According to the procedure described in the preparation of the pentaenone **23a**, Wittig reaction of phosphonium salt **4b** (409 mg, 0.84 mmol) with the dial **27** (100 mg, 0.46 mmol) and purification of the crude product by CC (acetone–CH_2Cl_2, 5 : 95) provided the analogue **2d** (125 mg, 42%) as a red solid; λ_{max}/nm 484; ν_{max}/cm^{-1} 3492 (OH), 1660 (conj. C=O), 1610, 1576 and 1550 (C=C); δ_H(500 MHz) 1.21 and 1.32 (each 6H, s, 1-*gem*-CH_3 and 1′-*gem*-CH_3), 1.81 (2H, t, *J* 13, 2-H_{ax} and 2′-H_{ax}), 1.94 (6H, s, 5-H and 5′-H), 1.98 and 2.00 (each 6H, s, 9-CH_3, 9′-CH_3, 13-CH_3 and 13′-CH_3), 2.15 (2H, dd, *J* 13 and 5, 2-H_{eq} and 2′-H_{eq}), 3.69 (2H, br s, OH × 2), 4.32 (2H, br dd, *J* 13.5 and 5.5, 3-H and 3′-H), 6.21 (2H, br d, *J* 16.5, 7-H and 7′-H), 6.25 and 6.29 (each 2H, br d, *J* 11.5, 10-H, 10′-H, 14-H and 14′-H), 6.38–6.48 (8H, m, 8-H, 8′-H, 12-H, 12′-H, 16-H, 16′-H, 17-H and 17′-H), 6.63 (4H, m, 11-H, 11′-H, 15-H and 15′-H); δ_C (125 MHz) 12.58 (9-CH_3 and 9′-CH_3), 12.80 (13-CH_3 and 13′-CH_3), 14.00 (5-CH_3 and 5′-CH_3), 26.16 and 30.76 (1-*gem*-CH_3 and 1′-*gem*-CH_3), 36.81 (C-1 and C-1′), 45.43 (C-2 and C-2′), 69.22 (C-3 and C-3′), 123.27 (C-7 and C-7′), 124.54 (C-11 and C-11′), 126.81 (C-5 and C-5′), 130.36 (C-15 and C-15′), 133.62, 134.16 and 134.59 (C-14, C-14′, C-16, C-16′, C-17 and C-17′), 134.52 (C-9 and C-9′), 135.22 (C-10 and C-10′), 136.60 (C-13 and C-13′), 139.77 (C-12 and C-12′), 142.38 (C-8 and C-8′), 162.26 (C-6 and C-6′), 200.43 (C-4 and C-4′) (Found: M^+, 648.4186. $C_{44}H_{56}O_4$ requires *M*, 648.4176).

Singlet-oxygen-quenching activities

A solution of the endoperoxide[3d,17] of 1,4-dimethylnaphthalene (40 mM in $CDCl_3$; 50 mm^3) was added to a mixture of TEMP (40 mM in $CDCl_3$; 50 mm^3), one of the analogues **2a**–**d** (0.01–10000 μM in $CDCl_3$; 50 mm^3) and $CDCl_3$ (50 mm^3), and the mixture was incubated at 37 °C for 2 min. Recording of the EPR spectrum of each mixture was started just after incubation, and an intensity (designated as *S*) of a signal originating from TEMP oxide radical[18] was measured. The intensities of signals from a control without any analogues (designated as *C*) and a blank (designated as *B*) with only TEMP were also measured. Quenching activity (designated as *Q*) of each analogue was calculated using equation (1).

$$Q\,(\%) = (C - S)/(C - B) \times 100 \qquad (1)$$

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