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C_{15}-Allenic Model Compounds for Carotenoids – Synthesis, Comparative ^{1}H NMR Data and a New Intramolecular Reaction

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The first synthesis of 2-*cis*-(4*R*)-5-[(2′*R*,4′*S*)-2′,4′-dihydroxy-2′,6′,6′-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol and 2-*cis*-(4*S*)-5-[(2′*S*,4′*S*)-2′,4′-dihydroxy-2′,6′,6′-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol via the previously undescribed 2-*cis*-5-[(1′*R*,2′*R*,4′*S*)-1′,2′-epoxy-4′-acetoxy-2′,6′,6′-trimethylcyclohex-1′-enyl]-3-methyl-2-penten-4-yn-1-yl acetate and 2-*cis*-5-[(1′*S*,2′*S*,4′*S*)-1′,2′-epoxy-4′-acetoxy-2′,6′,6′-trimethylcyclohex-1′-enyl]-3-methyl-2-penten-4-yn-1-yl acetate by a method analogous to that previously reported for the synthesis of the corresponding 2-*trans* compounds is described. The two 2-*trans* compounds were also prepared.

The four diastereomeric allenic triols were employed as ^{1}H NMR models for allenic carotenoids in a study of the effect on the chemical shift of the allenic proton. It was concluded that the individual effect of geometrical and allenic isomerisation are additive.

A new intramolecular dehydration reaction of 2-*cis*-(4*S*)-5-[(2′*S*,4′*S*)-2′,4′-dihydroxy-2′,6′,6′-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol involving the allene bond and leading to the formation of 2-*cis*-5-[(4′*R*)-4′-dihydroxy-2′,6′,6′-trimethylcyclohex-1′-enyl]-3-methyl-2,4-pentadienal was observed. A fully concerted reaction mechanism is discussed.

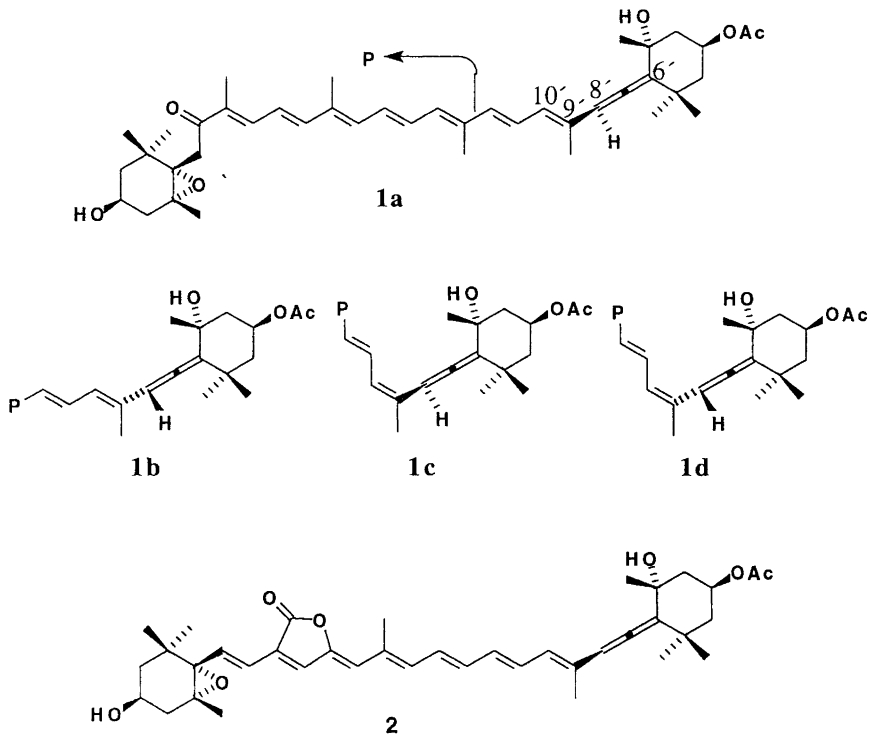
The formation of geometrical isomers of polyenes upon iodine catalysed photoisomerisation is well known.[1,2] All known naturally occurring allenic carotenoids have the *R* configuration at the chiral axis, cf. Ref. 3. Recently the generation, upon iodine catalysis under appropriate light conditions, of optical isomers of the allenic carotenoids fucoxanthin (**1**) and peridinin (**2**), see Scheme 1, with the *S* configuration at the chiral axis, was demonstrated for the first time.[4–6] A total of twelve stereoisomers of fucoxanthin (**1**)[5,7] and eight stereoisomers of peridinin (**2**),[6] including three *cis* isomers with the *S* configuration at the chiral allenic axis for both **1** and **2**, have been isolated from iodine-catalysed stereomutation mixtures, characterised and identified. Among the isomers of fucoxanthin (**1**) were all-*trans*-(6′*R*)- (**1a**), all-*trans*-(6′*S*)- (**1b**), 9′-*cis*-(6′*R*)- (**1c**) and 9′-*cis*-(6′*S*)-fucoxanthin (**1d**), see Scheme 1.

The main identification criteria for such stereoisomers include UV–VIS[1] and CD[8–10] in addition to detailed ^{1}H NMR spectroscopy. Average isomerisation shifts $\Delta = \delta_{cis} - \delta_{trans}$ in ^{1}H NMR spectroscopy have been reported for a number of different geometrical isomers of carotenoids, including di-, tri- and tetra-*cis* compounds.[11,12] For a mono-*cis* isomer or a di-*cis* isomer with sufficiently remote *cis* double bonds, a ca. 0.5 ppm downfield shift for an olefinic proton at C_n is compatible with a carbon–carbon *cis* double bond at position C_{n+1}, cf. refs. 11 and 12. Studies of relevant model compounds have demonstrated isomerisation shifts $\Delta = \delta_{(6S)} - \delta_{(6R)}$ for the allenic proton in allenic all-*trans* isomers in the range 0.02–0.17 ppm,[13] as subsequently confirmed for intact allenic carotenoids.[4–6]

Recent results for all-*trans*-(6′*S*)-(**1b**), 9′-*cis*-(6′*R*)- (**1c**) and 9′-*cis*-(6′*S*)-fucoxanthin (**1d**) suggested that the individual effects of *cis–trans* geometrical and *R*/*S* allenic isomerisation on the chemical shift of the allenic proton H-8′ are additive. It was considered of interest to confirm this observation by a study of relevant allenic model compounds.

Results and discussion

Bjørnland *et al.*[13] employed a series of allenic compounds in their study of the effect of the *R*/*S* allenic configuration of the chemical shift of the allenic proton H-8(8′) in carotenoids, including four optical isomers of the grasshopper ketone (**3**) and two optical isomers of the C_{15}-allenic triol

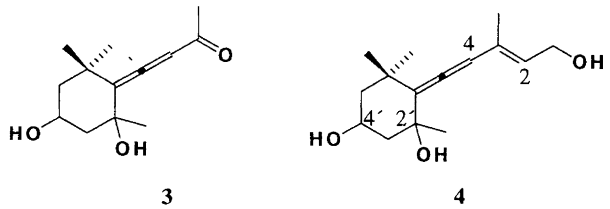


Scheme 1.

2-*trans*-5-(2,4-dihydroxy-2,6,6-trimethylcyclohexylidene)-3-methyl-2,4-pentadien-1-ol (**4**), see Scheme 2.

The C_{15}-allenic triol **4** was recently employed in the syntheses of mimulaxanthin[14,15] and peridinin (**2**).[16,17] A key intermediate in the synthesis of **4** was the C_{15}-acetylenic diacetate **5**.[14,16,17] With the 2-*trans* and 2-*cis* acetylenic diacetates **5a** and **5b** available from the recently reported total synthesis of all-*trans*[18,19] and 9-*cis*[20] acetylenic carotenoids, the C_{15}-allenic *trans* triol **4** with *R* or *S* configuration at the chiral axis and the corresponding 2-*cis* isomers were chosen as the target compounds in the present work.

Synthesis of optical and geometrical isomers of 5-(2',4'-dihydroxy-2',6',6'-trimethylcyclohexylidene)-3-methyl-2,4-pentadien-1-ol. The synthesis of the C_{15}-allenic 2-*trans* triols **4a** and **4b** was carried out according to the literature,[14,16] *cf.*, Scheme 3. The two diastereomeric 2-*trans*-(4*R*,2'*R*,4'*S*) **4a** and 2-*trans*-(4*S*,2'*S*,4'*S*) **4b** allenic triols were obtained as a 5:4 mixture from the 2-*trans* diacetate **5a**, via the two diastereomeric 2-*trans* epoxides **6a** and **6b**, in 9% overall yield. For convenience primed numbers are used for the cyclic end group of the C_{15}-model compounds throughout this paper. All spectroscopic data were in accordance with those reported.[16]

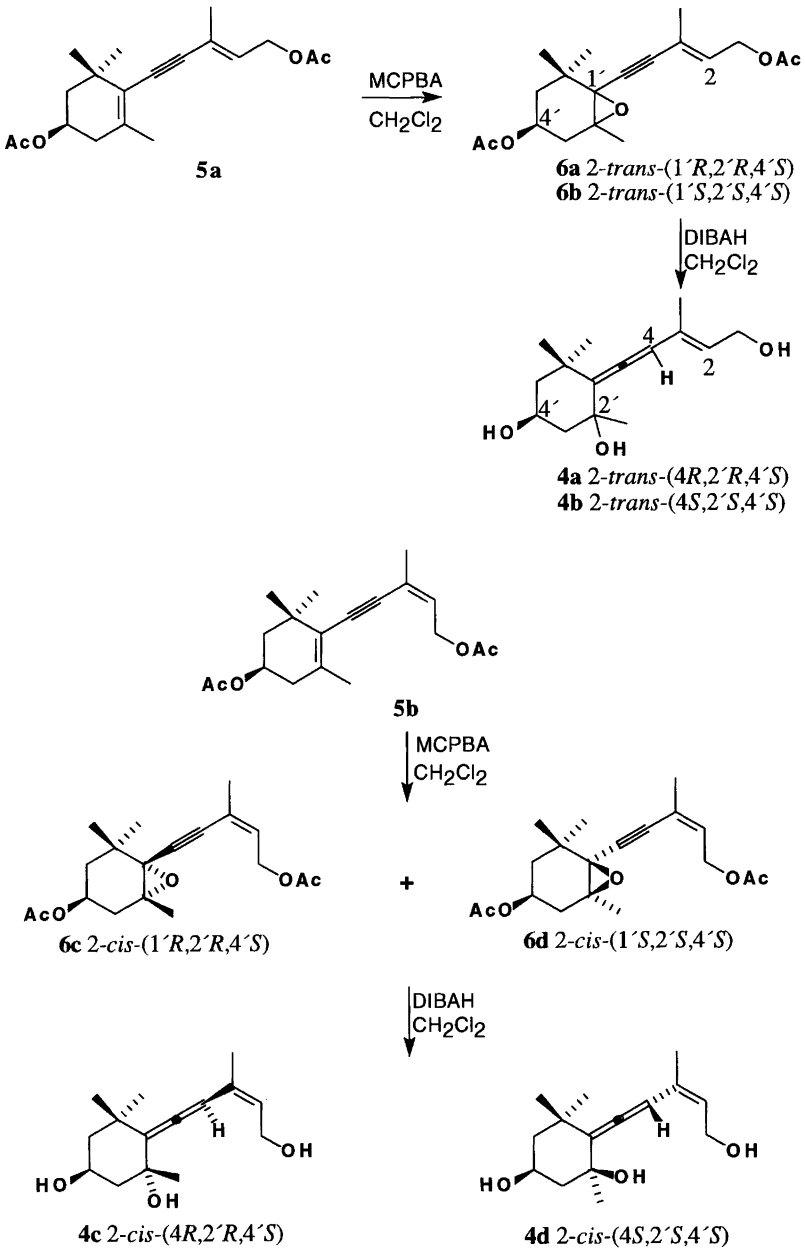


Scheme 2.

The two diastereomeric 2-*cis*-(4*R*,2'*R*,4'*S*) **4c** and 2-*cis*-(4*S*,2'*S*,4'*S*) **4d** allenic triols were synthesised in an analogous manner, see Scheme 3. Non-stereoselective epoxidation of the optically active 2-*cis* acetylenic diacetate **5b** with MCPBA afforded the diastereomeric epoxides **6c** and **6d** in 53% yield. Reduction of the mixture of the 2-*cis* epoxides **6c** and **6d** with DIBAH provided the diastereomeric allenic triols 2-*cis*-(4*R*,2'*R*,4'*S*) **4c** and 2-*cis*-(4*S*,2'*S*,4'*S*) **4d**, as a mixture, in 40% yield.

Spectroscopic analyses of the 2-*cis* epoxides **6c** and **6d** were carried out with a 5:4 mixture. All spectroscopic data were in accordance with the structures. Preparative TLC afforded the 2-*cis*-(4*R*,2'*R*,4'*S*) isomer **4c** in 9% overall yield and the 2-*cis*-(4*S*,2'*S*,4'*S*) isomer **4d** in 6% overall yield from **5b**. All spectroscopic data were in accordance with structures **4c** and **4d**.

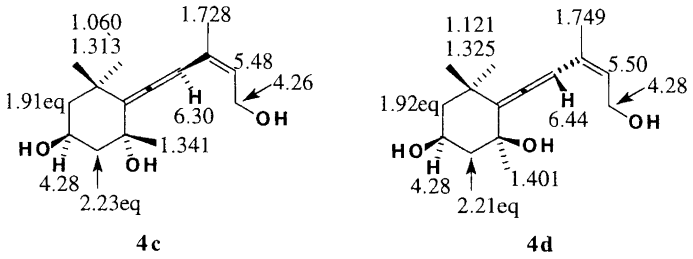
The present work represents the first syntheses of 2-*cis*-5-[(1'*R*,2'*R*,4'*S*)-1',2'-epoxy-4'-acetoxy-2',6',6'-trimethylcyclohex-1'-enyl]-3-methyl-2-penten-4-yn-1-yl acetate (**6c**), 2-*cis*-5-[(1'*S*,2'*S*,4'*S*)-1',2'-epoxy-4'-acetoxy-2',6',6'-trimethylcyclohex-1'-enyl]-3-methyl-2-pent-en-4-yn-1-yl acetate (**6d**), 2-*cis*-(4*R*)-5-[(2'*R*,4'*S*)-2',4'-dihydroxy-2',6',6'-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol (**4c**) and 2-*cis*-(4*S*)-5-[(2'*S*,4'*S*)-2',4'-dihydroxy-2',6',6'-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol (**4d**).



Scheme 3.

The synthesised diastereomeric triols differed in the stereochemical arrangement at one chiral centre (C-2′) and at the chiral axis (C-4), as a result of a complexation between the reducing agent and the epoxide moiety in the substrate.[16,21] All known allenic carotenoids have the same 5(5′)*R* configuration, corresponding to 2′*R* in **4**, at the asymmetric tertiary ring carbon atom, cf. Ref. 3. Despite this ambiguity, 2-*trans*-(4*R*,2′*R*,4′*S*)-**4** and 2-*trans*-(4*S*,2′*S*,4′*S*)-**4** have proved useful as ^{1}H NMR model compounds in studies of allenic isomers, cf. Ref. 13.

^{1}H NMR analysis of the allenic C_{15}-model compounds. Chemical shift assignments were based on ^{1}H–^{1}H COSY spectra. The ^{1}H NMR analyses of the 2-*trans* allenic triols **4a** and **4b** were performed with a 5:4 mixture of the two diastereomers. The chemical shift assignments were in accordance with previously reported data.[16] Assignments for the two 2-*cis* allenic triols **4c** and **4d** are given in Scheme 4. Isomerisation shifts for the allenic proton H-4 and the olefinic proton H-2, corresponding to H-8(8′) and H-10(10′) in allenic carotenoids, for the diastereomeric 2-*trans*-(4*S*,2′*S*,4′*S*) **4b**, 2-*cis*-(4*R*,2′*R*,4′*S*) **4c** and 2-*cis*-(4*S*,2′*S*,4′*S*) **4d** allenic triols relative to the 2-*trans*-(4*R*,2′*R*,4′*S*) **4a** isomer, are compiled in Table 1. The corresponding isomerisation shifts for all-*trans*-(6′*S*)- (**1b**), 9′-*cis*-(6′*R*)- (**1c**) and 9′-*cis*-(6′*S*)- (**1d**) relative to all-*trans*-(6′*R*)-fucoxanthin (**1a**) are included for comparison.



Scheme 4.

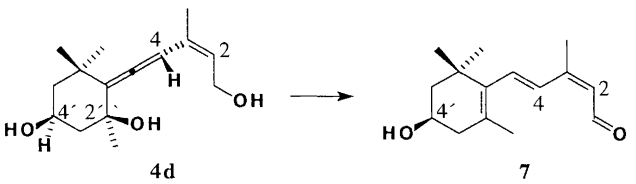
Table 1. Isomerisation shifts $\Delta = \delta_{isomer} - \delta_{all\text{-}trans\text{-}(R)\text{-allene}}$ for H-2 and H-4 in the allenic triols **4b**, **4b** and **4c** relative to **4a**, and for the corresponding protons H-10′ and H-8′ in all *trans*-(6′*S*)- (**1b**), 9′-*cis*-(6′*R*)- (**1c**) and 9′-*cis*-(6′*S*)- (**1d**) relative to all-*trans*-(6′*R*)-fucoxanthin (**1a**).

	$\Delta = \delta_{isomer} - \delta_{all\text{-}trans\text{-}(R)\text{-allene}}$					
Proton	**4b**	**4c**	**4d**	**1b**	**1c**	**1d**
H-2/H-10′	0.02	− 0.12	− 0.10	0.00	− 0.12	− 0.08
H-4/H-8′	0.15	0.35	0.49	0.10	0.52	0.62

Isomerisation shifts for the 2-*trans*-(4*S*,2′*S*,4′*S*) isomer **4b** were consistent with published data[13,16] for this compound. Furthermore, the results for the C_{15}-model compounds **4** were in good agreement with the results obtained for corresponding isomers of fucoxanthin (**1**), albeit with smaller isomerisation shifts for *cis–trans* rearrangement in the C_{15}-model compounds.

In conclusion, the present study confirmed the observation that the individual effects of *cis–trans* geometrical and *R*/*S* allenic isomerisation on the chemical shift of H-8(8′) in allenic carotenoids are additive.

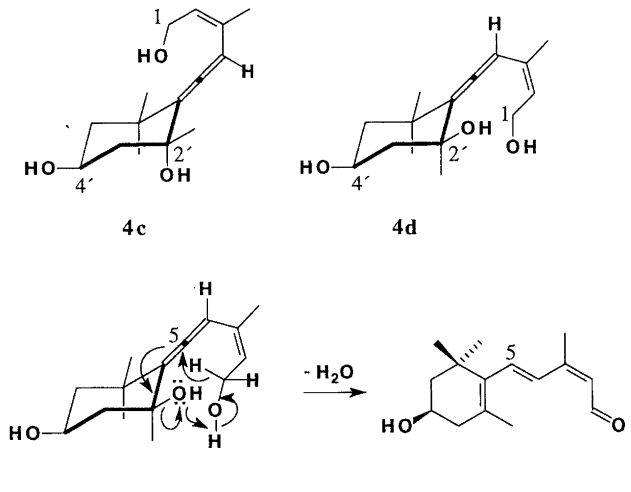
An intramolecular dehydration reaction of 2-cis-*(4S)-5-[(2′S,4′S)-2′,4′-dihydroxy-2′,6′,6′-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol involving the allene bond.* A mixture of the 2-*cis*-(4*R*,2′*R*,4′*S*) **4c** and 2-*cis*-(4*S*,2′*S*,4′*S*) **4d** allenic triols was not stable when kept as an oil. The initially white-yellow oil turned reddish-brown within ca. 10 days. Analytical TLC demonstrated that the 2-*cis*-(4*S*,2′*S*,4′*S*) **4d** isomer had disappeared and been replaced by a less polar compound. The almost quantitative conversion of the 2-*cis*-(4*S*,2′*S*,4′*S*) allenic triol **4d** to the less polar product under the above-described conditions, was further confirmed for a 85–90% pure sample of **4d**. The reaction product was identified as 2-*cis*-5-[(4′*R*)-4′-hydroxy-2′,6′,6′-trimethylcyclohex-1′-enyl]-3-methyl-2,4-pentadienal (**7**), see Scheme 5.



Scheme 5.

No reaction was observed when the 2-*cis*-(4*S*,2′*S*,4′*S*) allenic triol **4d** was kept in methanol or chloroform solution. This result indicated that the formation of **7** from **4d** was caused by an intermolecular reaction. On the other hand, the observation that **4d** reacted in the presence of, and without any effect on, **4c**, was consistent with an intramolecular reaction. Moreover, a mixture of the corresponding 2-*trans* allenic triols **4a** and **4b** and the ca. 90% pure 2-*cis*-(4*R*,2′*R*,4′*S*) diastereomer **4c** were stable when stored under conditions which promoted reaction of the 2-*cis*-(4*S*,2′*S*,4′*S*) allenic triol **4d**. Thus, an intramolecular rearrangement resulting in dehydration, favoured by the particular overall configuration/conformation of **4d**, appeared to be the most likely explanation for the present results. The stability of **4d** when dissolved may be explained by solvation effects.

Inspection of molecular models of the four allenic triols **4a–d** revealed that the intramolecular distance between the primary hydroxy group at C-1 and the tertiary hydroxy group at C-2′ in the 2-*cis* isomers **4c** and **4d** was considerably smaller than in the 2-*trans* isomers **4a** and **4b**. Furthermore, provided that the cyclohexylidene ring in **4c** and **4d** possesses a chair conformation with the secondary hydroxy group at C-4′ in an equatorial position, see Scheme 6, the resulting intramolecular distance between the primary hydroxy group at C-1 and the tertiary hydroxy group at C-2′ becomes distinctly smaller in the 2-*cis*-(4*S*) **4d** compared with the 2-*cis*-(4*R*) allene **4c**. The difference in intramolecular distance between the two hydroxy groups at C-1 and C-2′ is smaller for **4c** than for **4d** in the corresponding chair conformation with the secondary hydroxy group at C-4′ in an axial position. However, the latter chair conformation is clearly sterically hindered owing to 1,3-diaxial interactions. The coupling constants measured in the well resolved multiplet representing H-4′ in the ^{1}H NMR spectrum of the allenic triols **4a–d** were in the range 4–11 Hz, compatible with an



Scheme 6.

axial orientation of H-4′ and consequently an equatorial orientation for the secondary hydroxy group at C-4′. An equatorial orientation for H-4′ would, owing to the resulting dihedral angles, have caused small coupling constants of similar size (4–5 Hz)[22] to all of the four neighbouring methylene protons. Apparently the chair conformation with the secondary hydroxy group at C-4′ in an equatorial position represents the most stable conformation in both the 2-*trans* and 2-*cis* series.

A plausible reaction mechanism for an intramolecular reaction of the 2-*cis*-(4*S*,2′*S*,4′*S*) allenic triol **4d** to the 2-*cis*-(4′*R*) aldehyde **7**, is given in Scheme 6. A fully concentrated reaction is depicted. Since the reaction does not involve the secondary hydroxy group at C-4′, the resulting 2-*cis* hydroxy aldehyde **7** should have the 4′*R* configuration, as confirmed by a comparison of the optical rotation [α] for **7** with that of 2-*trans*-(4′*R*)-4′-hydroxy-β-ionone.[23]

Experimental

General methods. All solvents were of *p.a.* quality. Dichloromethane was dried over freshly activated 3 Å molecular sieves. Solvents were evaporated under reduced pressure at 20–35°C.

Thin layer chromatography was carried out on silica gel 60 F_{254} (Merck Art. 5554) with ethyl acetate–heptane 1:1 (system 1) or pure ethyl acetate (system 2) as eluents. Column chromatography was performed on silica gel 60 (Merck Art. 7734) with mixtures of hexane–ethyl acetate as eluents. High performance liquid chromatography was carried out on a Hewlett Packard series 1050 instrument and a Spherisorb S 5-W silica column using 5% methanol in dichloromethane as the eluent, flow = 1.0 ml min^{-1}. Simultaneous detection at 250, 280, 320, 350, 380 and 450 nm was employed.

UV–VIS spectra were recorded on a Perkin Elmer 552 spectrophotometer, solvents are specified in each case. Spectral fine structure is expressed as %III/II.[24] IR spectra were recorded of liquids as films between NaCl discs, on a Nicolet 20 SXC FT-IR spectrophotometer. Mass spectra were recorded on an AEI 902 spectrometer with direct inlet to the ion source. ^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY spectra were recorded on a 400 MHz (100 MHz for ^{13}C) Jeol EX-400 instrument for samples in $CDCl_3$ solution.

Synthesis of 2-trans-(4R)-5-[(2′R,4′S)-2′,4′-dihydroxy-2′,6′,6′-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol *and* 2-trans-(4S)-5-[(2′S,4′S)-2′,4′-dihydroxy-2′,6′,6′-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol

2-trans-5-[(1′R,2′R,4′S)-1′,2′-epoxy-4′-acetoxy-2′,6′,6′-trimethylcyclohex-1′-enyl]-3-methyl-2-penten-4-yn-1-yl acetate (**6a**) *and* 2-trans-5-[(1′S,2′S,4′S)-1′,2′-epoxy-4′-acetoxy-2′,6′,6′-trimethylcyclohex-1′-enyl]-3-methyl-2-penten-4-yn-1-yl acetate (**6b**). The two diastereomeric epoxides **6a** and **6b** were prepared according to a published procedure.[16] MCPBA (1.25 g, 7.22 mol) in dichloromethane (16 ml) was added dropwise to a solution of the available 2-*trans*-5-[(4′*R*)-4′-acetoxy-2′,6′,6′-trimethylcyclohex-1′-enyl]-3-methyl-2-penten-4-yn-1-yl acetate[18] (**5a**, 1.53 g, 4.81 mmol) in dichloromethane (16 ml) at 4°C, under an N_2 atmosphere in the dark. The reaction was monitored by TLC (system 1). After 5 h was the reaction mixture poured over a cold (4°C) saturated solution of sodium bicarbonate, and the products were extracted with dichloromethane. The organic phase was washed with water, dried over anhydrous sodium and the solvents were evaporated. The resulting residue was dissolved in a minimum volume of benzene and subjected to CC with gradient elution, hexane–ethyl acetate 9:1 to 7:3. The two diastereomeric epoxides **6a** and **6b** were obtained in a ca. 1:1 mixture as a light yellow oil, in 21% yield (0.34 g, 1.02 mmol). The HPLC system employed did not separate **6a** and **6b**. No contaminant was detected in the HPLC analysis. The spectroscopic analyses were carried out with the CC purified mixture.

UV λ_{max} (ethanol) 229 nm; IR (KBr) cm^{-1} 2966–2873m (CH), 2216w (C≡C), 1739s (acetate), 1370m, 1240s (acetate), 1030m; MS [IP 50 eV, 170°C; *m/z* (% rel.int.)]; 274 (4, [*M* − 60]), 258 (4, [*M* − 16 − 60]), 218 (8), 198 (6, [*M* − 16 − 60 − 60]), 173 (8), 156 (11), 148 (15), 139 (9), 105 (6), 60 (15), 43 (100); ^{1}H NMR ($CDCl_3$) **6a**: δ 1.147 (s, 3 H, Me-6′), 1.250 (s, 3 H, Me-6′), 1.38 (dd, 1 H, *J* 7.7 Hz, *J* 13.2 Hz, H-5′ax), 1.494 (s, 3 H, Me-2′), 1.63 (m, 1 H, H-5′eq), 1.81 (m, 1 H, H-3′ax), 1.866 (s, Me-3), 2.005 (s, 3 H, Me in AcO), 2.066 (s, Me in AcO), 2.38 (m, 1 H, H-3′eq), 4.63 (d, *J* 7.3 Hz, H-1), 4.86 (m, H-4′), 5.93 (tq, *J* 1.0 Hz, *J* 7.0 Hz, H-2); ^{1}H NMR ($CDCl_3$) **6b**: δ 1.178 (s, 3 H, Me-6′), 1.221 (s, 3 H, Me-6′), 1.41 (m, 1 H, H-5′ax), 1.463 (s, 3 H, Me-2′), 1.58 (m, 1 H, H-5′eq), 1.84 (m, 1 H, H-3′ax), 1.866 (s, Me-3), 2.010 (s, 3 H, Me in AcO),

2.066 (s, Me in AcO), 2.33 (m, 1 H, H-3'eq), 4.63 (d, *J* 7.3 Hz, H-1) 4.86 (m, H-4'), 5.93 (tq, *J* 1.0 Hz, *J* 7.0 Hz, H-2).

*2-*trans*-(4R)-5-[(2'R,4'S)-2',4'-Dihydroxy-2',6',6'-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol* (**4a**) *and* 2-trans*-(4S)-5-[(2'S,4'S)-2',4'-dihydroxy-2',6',6'-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol* (**4b**). The two diastereomeric allenic triols **4a** and **4b** were prepared essentially according to a published procedure.[16] The preceding 1:1 mixture of the two epoxides **6a** and **6b** (0.29 g, 0.87 mmol) was dissolved in dry dichloromethane (20 ml) and the mixture was cooled to 0°C. A solution of DIBAH in dichloromethane (1.0 M, 7 ml, 7 mmol) was added dropwise under an N_2 atmosphere. The mixture was stirred at 0–10°C for 1.5 h under an N_2 atmosphere. A cold (4°C) saturated solution of ammonium chloride was added carefully and the water phase was extracted several times with dichloromethane. The organic phase was washed with a saturated solution of sodium bicarbonate and water, dried over anhydrous sodium sulphate and the solvents were evaporated off, to yield the 2-*trans* allenic triols **4a** and **4b** as a yellow–white viscous oil, in 40% yield (87.0 mg, 0.35 mmol). HPLC of the residue indicated a 5:4 mixture of the two diastereomers. Attempts to separate **4a** and **4b** by preparative TLC (system 1 or 2) were not successful. The spectroscopic analyses were carried out with the TLC purified 5:4 mixture.

UV λ_{max} (ethanol) 225 nm; IR (KBr) cm^{-1} 3380s (OH), 2963–2870m (CH), 1937m (C=C=C), 1431m, 1373m, 1152m, 1019m; MS [IP 50 eV, 160°C; *m/z* (% rel. int.)]: 252 (1, [*M*]), 234 (12, [*M* – 18]), 219 (4), 216 (2, [*M* – 18 – 18]), 175 (6), 161 (10), 147 (12), 135 (13), 121 (12), 109 (25), 95 (25), 43 (100); ^{1}H NMR ($CDCl_3$) **4a**: δ 1.060 (s, 3 H, Me-6'), 1.24–1.42 (m, H-3'ax and H-5'ax), 1.322 (s, Me-6'), 1.343 (s, 3 H, Me-2'), 1.678 (s, 3 H, Me-3), 1.94 (m, H-5'eq), 2.24 (m, H-3'eq), 4.26 (d, *J* 6.8 Hz, H-1), 4.30 (tt, *J* 3.9 Hz, *J* 11.2 Hz, H-4'), 5.60 (t, *J* 7.3 Hz, H-2), 5.95 (s, 1 H, H-4); ^{1}H NMR ($CDCl_3$) **4b**: δ 1.115 (s, 3 H, Me-6'), 1.24–1.42 (m, H-3'ax and H-5'ax), 1.322 (s, Me-6'), 1.393 (s, 3 H, Me-2'), 1.689 (s, 3 H, Me-3), 1.94 (m, H-5'eq), 2.24 (m, H-3'eq), 4.26 (d, *J* 6.8 Hz, H-1), 4.30 (tt, *J* 3.9 Hz, *J* 11.2 Hz, H-4'), 5.62 (t, *J* 7.3 Hz, H-2), 6.10 (s, 1 H, H-4).

Synthesis of 2-cis*-(4R)-5-[(2'R,4'S)-2',4'-dihydroxy-2',6',6'-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol and* 2-cis*-(4S)-5-[(2'S,4'S)-2',4'-dihydroxy-2',6',6'-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol*

*2-*cis*-5-[(1'R,2'R,4'S)-1',2'-Epoxy-4'-acetoxy-2',6',6'-trimethylcyclohex-1'-enyl]-3-methyl-2-penten-4-yn-1-yl acetate* (**6c**) *and* 2-cis*-5-[(1'S,2'S,4'S)-1',2'-epoxy-4'-acetoxy-2',6',6'-trimethylcyclohex-1'-enyl]-3-methyl-2-penten-4-yn-1-yl acetate* (**6d**). The two diastereomeric epoxides **6c** and **6d** were prepared by a procedure similar to that employed for the corresponding 2-*trans* epoxides **6a** and **6b** above. MCPBA (2.05 g, 11.9 mmol) in dichloromethane (20 ml) was added dropwise to a solution of the available 2-*cis*-5-[(4'*R*)-4'-acetoxy-2',6',6'-trimethylcyclohex-1'-enyl]-3-methyl-2-penten-4-yn-1-yl acetate[18] (**5b**, 3.0 g, 9.4 mmol) in dichloromethane (30 ml) at 4°C, under an N_2 atmosphere in the dark. The reaction was monitored by TLC (system 1). After 20 h was the reaction mixture poured into a cold (4°C) saturated solution of sodium bicarbonate, and the products were extracted with dichloromethane.

Treatment as described above for the 2-*trans* analogues afforded he two diastereomeric epoxides **6c** and **6d** in a ca. 4:5 mixture as a light yellow oil, in 53% yield (1.66 g, 5.0 mmol). The HPLC system employed did not separate the two diastereomers. No contaminant was detected in the HPLC analysis. The spectroscopic analyses were carried out with the CC purified mixture.

UV λ_{max} (ethanol) 231 nm; IR (KBr) cm^{-1} 2967–2872m (CH), 2214 and 2181w (C≡C), 1740s (acetate), 1370m, 1240s (acetate), 1029m; MS [IP 40 eV, 180°C; *m/z* (% rel. int.)]: 334 (2, [*M*]), 274 (9, [*M* – 60]), 258 (3, [*M* – 16 – 60]), 248 (6), 218 (17), 198 (2, [*M* – 16 – 60 – 60]), 189 (18), 173 (13), 156 (14), 148 (6), 139 (36), 105 (9), 43 (100); ^{1}H NMR ($CDCl_3$) **6c**: δ 1.159 (s, 3 H, Me-6'), 1.261 (s, 3 H, Me-6'), 1.38 (m, 1 H, H-5'ax), 1.506 (s, 3 H, Me-2'), ca. 1.60 (m, 1 H, H-5'eq), ca. 1.80 (m, 1 H, H-3'ax), 1.907 (s, Me-3), 2.013 (s, 3 H, Me in AcO), 2.053 (s, Me in AcO), 2.38 (dd, 1 H, *J* 4.9 Hz, *J* 10.3 Hz, H-3'eq), 4.73 (d, *J* 7.3 Hz, H-1), 4.87 (m, H-4'), 5.82 (tq, *J* 1.5 Hz, *J*≈7 Hz, H-2); ^{1}H NMR ($CDCl_3$) **6d**: δ 1.192 (s, 3 H, Me-6'), 1.236 (s, 3 H, Me-6'), 1.41 (m, 1 H, H-5'ax), 1.478 (s, 3 H, Me-2'), ca. 1.55 (m, 1 H, H-5'eq), ca. 1.80 (m, 1 H, H-3'ax), 1.907 (s, Me-3), 2.001 (s, 3 H, Me in AcO), 2.053 (s, Me in AcO), 2.33 (dd, 1 H, *J* 6.4 Hz, *J* 14.8 Hz, H-3'eq), 4.73 (d, *J* 7.3 Hz, H-1), 4.87 (m, H-4'), 5.82 (tq, *J* 1.5 Hz, *J*≈7 Hz, H-2).

*2-*cis*-(4R)-5-[(2'R,4'S)-2',4'-Dihydroxy-2',6',6'-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol* (**4c**) *and* 2-cis*-(4S)-5-[(2'S,4'S)-2',4'-dihydroxy-2',6',6'-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol* (**4d**). The two diastereomeric allenic triols **4c** and **4d** were synthesised in a way similar to that described for the corresponding 2-*trans* allenic triols **4a** and **4b** above. The preceding 4:5 mixture of the two epoxides **6c** and **6d** (0.5 g, 1.5 mmol) was dissolved in dry dichloromethane (30 ml) and the mixture was cooled to 0°C. A solution of DIBAH in dichloromethane (1.0 M, 12 ml, 12 mmol) was added dropwise under an N_2 atmosphere. The mixture was stirred at 0–10°C for 1.5 h under an N_2 atmosphere. A cold (4°C) saturated solution of ammonium chloride was added carefully and the water phase was extracted several times with dichloromethane. The organic phase was washed with a saturated solution of sodium bicarbonate and water, dried over anhydrous sodium sulphate and the solvents were evaporated off. HPLC of the residue indicated a 5:4 mixture of the two diastereomers. Preparative

TLC (system 2) afforded the 2-*cis*-(4*R*,2′*R*,4′*S*) allenic triol **4c** (R_f = 0.16) in 17% yield (64.3 mg, 0.26 mmol, > 90% pure as demonstrated by ^{1}H NMR spectroscopy) and the 2-*cis*-(4*S*,2′*S*,4′*S*) isomer **4d** (R_f = 0.31) in 11% yield (41.1 mg, 0.17 mmol, > 85% pure as demonstrated by ^{1}H NMR spectroscopy). Attempted crystallisation of **4c** and **4d** from methanol–diethyl ether or methanol–pentane was not successful. IR and mass spectra were recorded of the 5:4 mixture.

IR (KBr) cm^{-1} 3365s (OH), 2963–2870m (CH), 1937m (C = C = C), 1708, m, 1453m, 1368m, 1019m; MS [IP 30 eV, 180°C; *m/z* (% rel. int.)]: 252 (2, [*M*]), 234 (25, [*M* − 18]), 219 (12), 216 (3, [*M* − 18 − 18]), 175 (12), 161 (36), 147 (25), 135 (42), 121 (29), 119 (30), 109 (62), 95 (40), 91 (29), 83 (22), 43 (100); **4c**: UV λ_{max} (ethanol) 227 nm; ^{1}H NMR ($CDCl_3$): δ 1.060 (s, 3 H, Me-6′), 1.23 (m, 1 H, H-5′ax), 1.313 (s, 3 H, Me-6′), 1.341 (s, 3 H, Me-2′), 1.38 (m, 1 H, H-3′ax), 1.728 (s, 3 H, Me-3), 1.91 (m, 1 H, H-5′eq), 2.23 (m, 1 H, H-3′eq), 4.26 (d, 2 H, *J* 7.2 Hz, H-1), 4.28 (tt, 1 H, *J* 3.8 Hz, *J* 11.1 Hz, H-4′), 5.48 (t, *J* 7.3 Hz, H-2), 6.30 (s, 1 H, H-4); **4d**: UV λ_{max} (ethanol) 227 nm; ^{1}H NMR ($CDCl_3$): δ 1.121 (s, 3 H, Me-6′), 1.20–1.40 (m, H-3′ax and H-5′ax), 1.325 (s, 3 H, Me-6′), 1.401 (s, 3 H, Me-2′), 1.749 (s, 3 H, Me-3), 1.92 (m, 1 H, H-5′eq), 2.21 (m, 1 H, H-3′eq), 4.28 (d, 2 H, *J* 7.1 Hz, H-1), ca. 4.30 (tt, 1 H, *J* 3.8 Hz, *J* 11.1 Hz, H-4′), 5.50 (t, 1 H, *J* 7.3 Hz, H-2), 6.44 (s, 1 H, H-4).

An intramolecular dehydration reaction of 2-cis-*(4S)-5-[(2′S,4′S)-2′,4′-dihydroxy-2′,6′,6′-trimethylcyclohexylidene]-3-methyl-2,4-pentadien-1-ol.* The 2-*trans* allenic triols **4a** and **4b** and the 2-*cis*-(4*R*,2′*R*,2′*S*) allenic triol **4c** were stable when stored as oils or dissolved in a solvent. The 2-*cis*-(4*S*,2′*S*,4′*S*) allenic triol **4d** was stable when stored in methanol solution at −20°C or 4°C or in chloroform at 20°C, but reacted slowly over 10 days to give a less polar product when stored as an oil at 4°C. In a quantitative experiment, the 2-*cis*-(4*S*,2′*S*,4′*S*) allenic triol **4d** (62.0 mg, 0.25 mmol) provided a less polar product identified as 2-*cis*-5-[(4′*R*)-4′-hydroxy-2′,6′,6′-trimethylcyclohex-1′-enyl]-3-methyl-2,4-pentadienal (**7**) in 84% yield (48.1 mg, 0.21 mmol) when stored as an oil at 4°C for seven days.

UV λ_{max} (ethanol) 272 nm; MS [IP 40 eV, 180°C; *m/z* (% rel. int.)]: 234 (20, [*M*]), 216 (7, [*M* − 18]), 201 (15), 248 (6), 193 (15), 187 (15), 189 (18), 175 (15), 167 (12), 149 (36), 121 (31), 105 (32), 95 (50), 91 (35), 43 (100); ^{1}H NMR ($CDCl_3$): δ 1.084 (s, 6 H, Me-6′), 1.47 (m, 1 H, H-5′ax), 1.738 (s, 3 H, Me-2′), 1.78 (m, 1 H, H-5′eq), 2.05 (m, 1 H, H-3′ax), 2.309 (s, 3 H, Me-3), 2.41 (dd, 1 H, *J* 5.4 Hz, *J* 17.6 Hz, H-3′eq), 4.00 (m, 1 H, H-4′), 5.94 (d, 1 H, *J* 7.8 Hz, H-2), 6.20 (d, 1 H, *J* 16.1 Hz, H-5), 6.67 (d, 1 H, *J* 16.1 Hz, H-4), 10.13 (d, 1 H, *J* 7.8 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 12.9 (Me-3), 21.6 (Me-2′), 28.7 and 30.2 (Me-6′), 36.9 (C-1′), 42.5 (C-3′), 48.2 (C-5′), 64.7 (C-4′), 129.1 (C-2), 129.3 [C-2′(?)], 134.5 (C-4), 136.5 (C-5), 136.7 [C-1′(?)], 154.2 [C-3(?)], 191.4 (C-1); $[\alpha]_D^{23} = -70.5°$, *c* = 0.006 (MeOH), cf. $[\alpha]_D^{20}$ (3*R*)-3-hydroxy-β-ionone) = −76.8°, *c* = 1.08% ($CHCl_3$).[23]

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