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Total Synthesis of C_{31}-Methyl Ketone Apocarotenoids: Sintaxanthin and (3*R*)-3-Hydroxysintaxanthin

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The previously undescribed (all-*E*)-2,7,11-trimethyl-12-oxo-2,4,6,8,10-tridecapentenal has been synthesised in 26% overall yield in six steps from the readily available 3-methyl-2-penten-4-yn-1-ol and 2,7-dimethyl-2,4,6-octatrienedial.

This C_{16}-keto aldehyde was used in the first total synthesis of fully characterised (all-*E*)-sintaxanthin and optically active (all-*E*)-(3*R*)-3-hydroxysintaxanthin.

The C_{16}-keto aldehyde is a versatile building block for any C_{31}-methyl ketone apocarotenoid.

Some fifty naturally occurring apocarotenoids[1] with abbreviated carbon skeletons have been reported.[2] Twelve of these are methyl ketones.[2]

The C_{33}-methyl ketones citranaxanthin and reticulataxanthin and the corresponding β-hydroxy ketones are believed to be isolation artifacts formed by aldol condensation of C_{30}-carotenals with acetone.[3] Tangeraxanthin has been tentatively assigned a C_{34}- *retro* structure.[4] The remaining seven methyl ketones represent natural C_{31}-apocarotenoids. Paracentrone[5] and 19-hexanoyloxyparacentrone 3-acetate[6,7] are allenic and hopkinsiaxanthin[8] and triophaxanthin[9] acetylenic.

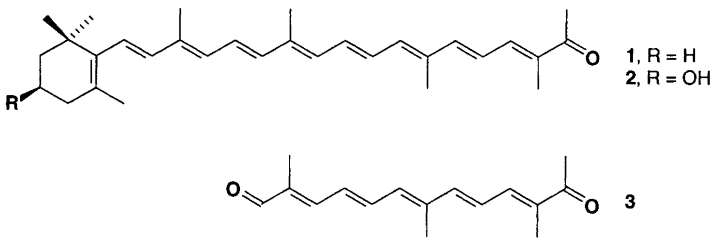
Sintaxanthin (**1**, Scheme 1) and 3-hydroxysintaxanthin (**2**) have been reported to be isolated from various citrus fruits.[10–13] A partial synthesis of **1** from the corresponding C_{30}-aldehyde β-citraurin with methyllithium followed by allylic oxidation has been reported,[10] but no total synthesis of any of the C_{31}-methyl ketone apocarotenoids have so far been published.

In this paper the total synthesis of sintaxanthin (**1**) and optically active (3*R*)-3-hydroxysintaxanthin (**2**) are reported. A $C_{15} + (C_{10} + C_6) = C_{31}$ strategy was chosen with the previously undescribed 2,7,11-trimethyl-12-oxo-2,4,6,8,10-tridecapentaenal (**3**, Scheme 1) as the C_{16} key intermediate. With this C_{16}-keto aldehyde as a general building block the total synthesis of other C_{31}-skeletal methyl ketone apocarotenoids may be pursued.

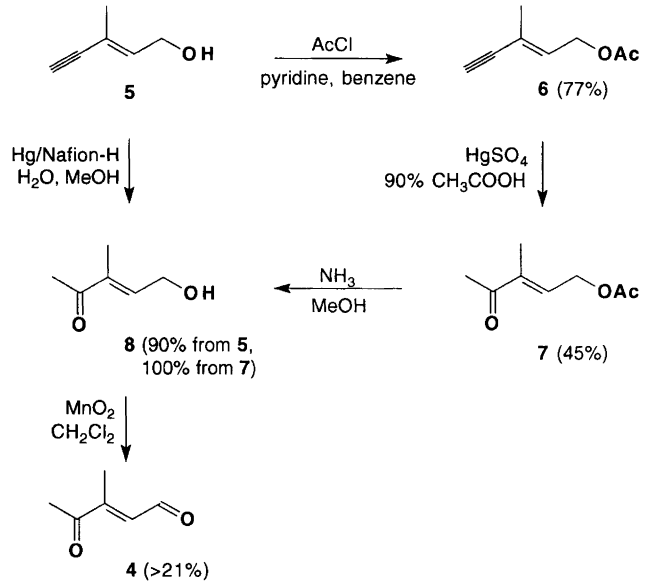
Results and discussion

Synthesis of the C_6-keto aldehyde **4**. Samokhvalov *et al.*[14] have reported the synthesis of the C_6-keto aldehyde **4**, Scheme 2, from the acetylenic alcohol **5** in four steps with an overall yield of 14%. Kubota and Takeshima[15] synthesised **4** in two steps from 3-oxobutan-2-one in 3% overall yield.

The present synthesis of **4** by two different routes is illustrated in Scheme 2. The four-step route is similar to that published by Samokhvalov *et al.*[14] The hydroxy group in the acetylenic alcohol **5** was protected by acetylation. Addition of water to the triple bond of **6** with mercuric sulfate as the catalyst gave the acetylated ketone **7**. Removal of the protective group furnished the hydroxy ketone **8** in improved (35%) yield from the acetylenic alcohol **5**.



Scheme 1.



Scheme 2.

The hydroxy ketone **8** has also been synthesized directly in 90% yield from the acetylenic alcohol **5** with Hg–Nafion-H[16,17] as the catalyst in aqueous methanol.

Allylic oxidation of **8** with manganous dioxide afforded the C_6-keto aldehyde **4**. The maximum isolated yield in this reaction was 21%. Problems associated with the volatility and stability of **4** are reported in the Experimental part.

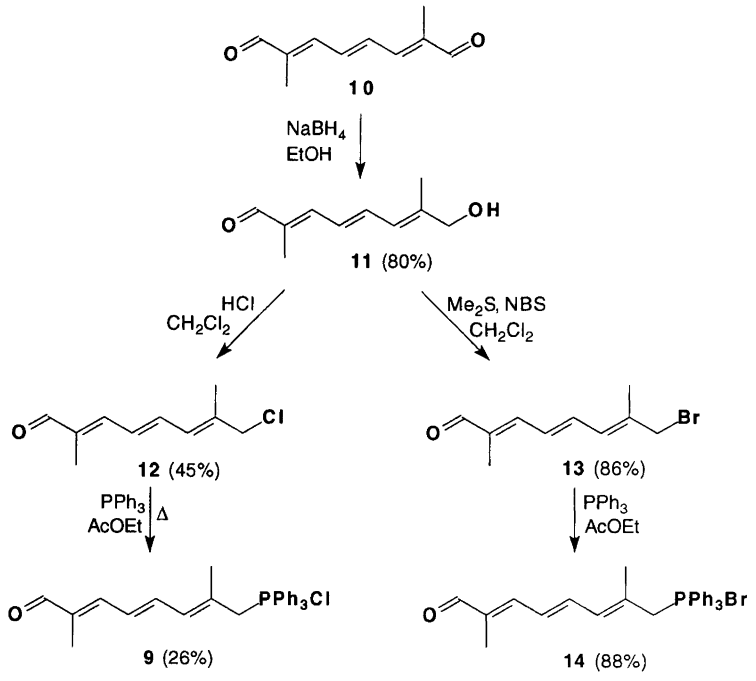
The boiling point reported Samokhvalov *et al.*[14] is not compatible with the fully characterised (GLC, UV–VIS, IR, MS, ^{1}H NMR data) keto aldehyde **4**.

Synthesis of the C_{16}-keto aldehyde **3**. The C_{10}-phosphonium salt **9**, Scheme 3, was first synthesised by Bernhard *et al.*[18] in 40% yield from the symmetrical C_{10}-dial **10**. Pattenden *et al.*[19] reported the partial reduction of the C_{10}-dial with sodium borohydride in methanol.

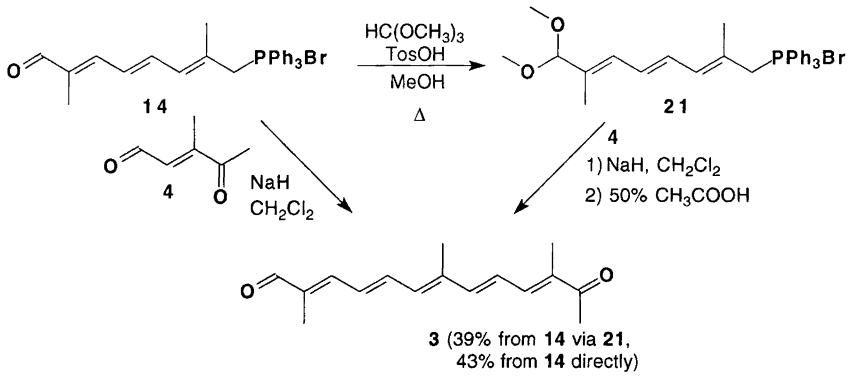
In this work, the C_{10}-dial **10** was partially reduced with sodium borohydride in ethanol yielding 80% crystalline **11** after column chromatography (CC) and crystallisation from diethyl ether. Chlorination of **11** with hydrogen chloride, followed by reaction of the chloride **12** with triphenylphosphine in refluxing ethyl acetate afforded the phosphonium salt **9** in 9% overall yield from the C_{10}-dial (**10**), see Scheme 3.

Corey *et al.*[20] have reported a mild procedure for substituting *primary* and *secondary* allylic or benzylic hydroxy groups with halogen. The method involves addition of dimethyl sulfide to *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS), generating free halide anions. The bromide **13** was obtained in 86% yield by this procedure. Reaction of **13** with triphenylphosphine in ethyl acetate at 20°C furnished the phosphonium salt **14** in 88% yield, or 61% overall yield from the C_{10}-dial **10**, see Scheme 3.

Bernhard *et al.*[18] used the C_{10}-phosphonium salt **9** in their synthesis of optically active 7,8-didehydroastaxanthin. Prior to the Wittig reaction, the aldehyde function of **9** was protected as an acetal. By similar protection of the aldehyde moiety of **14**, carrying out the Wittig



Scheme 3.



Scheme 4.

reaction with the C_6-keto aldehyde **4** and deprotecting the aldehyde in aqueous acetic acid, the key intermediate C_{16}-keto aldehyde **3** was obtained in 39% yield, see Scheme 4.

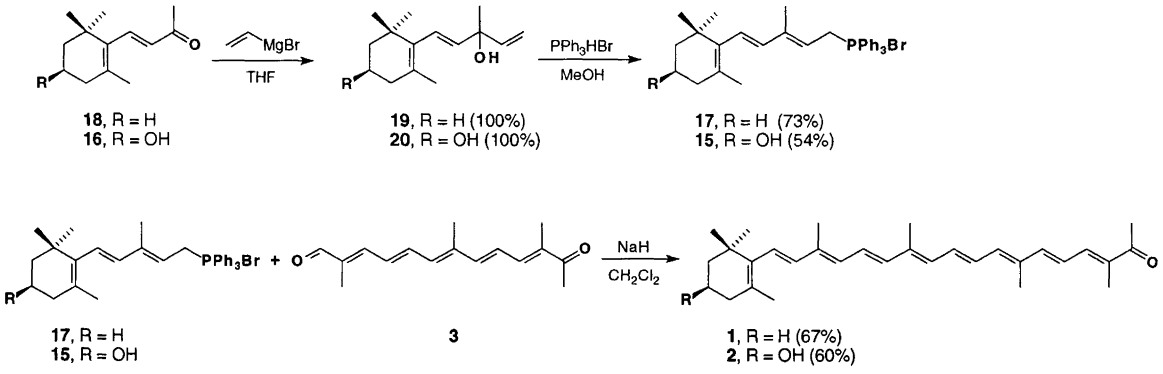
However, protection of the aldehyde moiety of **14** proved not to be necessary. Direct Wittig reaction between **4** and **14** afforded the C_{16}-keto aldehyde **3** in 43% yield, see Scheme 4. The procedure involving the extra reactions of protecting and deprotecting the aldehyde moiety gave a ca. 1:1 mixture of all-*E*-**3** and different *Z* isomers. However, the direct approach provided a 7:3 mixture of all-*E*-**3** and *Z* isomers. The pure all-*E*-isomer of **3** was crystallised from acetone–hexane.

*Synthesis of sintaxanthin (***1***) and 3-hydroxysintaxanthin (***2***).* Loeber *et al.*[21] first synthesised the optically inactive C_{15}-hydroxylated phosphonium salt **15** (Scheme 5) from 3-hydroxy-β-ionone (**16**, carotenoid numbering) in 58% yield. A similar approach was used in this work for the synthesis of the phosphonium salts **15** and **17**. Grignard reaction between β-ionone (**18**) and vinylmagnesium bromide afforded the *tertiary* alcohol **19**, which upon reaction with triphenylphosphine hydrobromide in methanol furnished the crystalline phosphonium salt **17** in an overall yield of 73%, see Scheme 5. A similar reaction sequence gave the optically active hydroxylated phosphonium salt **15** in 54% overall yield from optically active (3*R*)-3-hydroxy-β-ionone (**16**) via the diol **20**, see Scheme 5. The synthesis of the optically active phosphonium salt **15** by the same approach via **20**[22,23] and by a different route[24] has been reported.

Wittig reaction of the C_{15}-phosphonium salt **17** with the C_{16}-keto aldehyde **3** provided sintaxanthin (**1**) in 67% yield, see Scheme 5. The overall yield of **1** was 18% based on the symmetrical C_{10}-dial **10**. Sintaxanthin (**1**) was obtained as a 3:1 mixture of the all-*E* compound and three different *Z* isomers. Pure (all-*E*)-sintaxanthin (**1**) was obtained by repeated crystallisation from methanol–diethyl ether.

3-Hydroxysintaxanthin (**2**) was obtained in 60% yield by a Wittig reaction between the C_{15}-hydroxylated phosphonium salt **15** and the C_{16}-keto aldehyde **3**. The overall yield of **2** was 16% based on the symmetrical C_{10}-dial **10**. 3-Hydroxysintaxanthin (**2**) was obtained as a mixture of all-*E*-**2** (73%) and two *Z* isomers (13 + 14%). The pure, optically active (all-*E*)-(3*R*)-3-hydroxysintaxanthin (**2**) was obtained by repeated crystallisation from methanol–diethyl ether.

Both (all-*E*)-sintaxanthin (**1**) and (all-*E*)-(3*R*)-3-hydroxysintaxanthin (**2**) were fully characterised by MS, VIS, m.p. and IR, ^1H and ^{13}C NMR spectroscopy. Assignments of the ^1H and ^{13}C NMR spectra were based on ^1H–^1H COSY and on NMR data for different carotenoid end groups, published by Englert.[25] (all-*E*)-(3*R*)-hydroxy-



Scheme 5.

sintaxanthin (**2**) was, in addition, characterised by CD spectroscopy. The CD spectrum of **2** displayed a Cotton effect similar to that of (all-*E*)-(3*R*, 3′*R*)-zeaxanthin,[26] but with lower Δε-values, confirming the 3*R*-configuration at C-3.

Experimental

General methods. Solvents were of distilled or *p.a.* quality. Diethyl ether (ether) used for extraction was chromatographed through alumina (neutral). Diethyl ether and tetrahydrofuran (THF) used as solvents in reactions were distilled over solid sodium. Sodium hydride was washed with hexane before use. Solutions were dried over anhydrous sodium sulfate. Dichloromethane was dried over freshly activated 3 Å molecular sieves. Solvents were evaporated under reduced pressure. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck Art. 5554) with ethyl acetate–heptane 2:3 (system 1) or 1:1 (system 2) as eluents. Column chromatography (CC) was performed on silica gel 60 (Merck Art, 7734) with mixtures of ethyl acetate and heptane as eluents. High performance liquid chromatography (HPLC) was carried out on a Hewlett Packard series 1050 instrument and a 5μ Brownlee silica column. Eluents were 5% methanol in dichloromethane, flow = 1 ml min^{-1} (system 1), hexane–dichloromethane–2-propanol 90:7:3 plus 0.1% *N*-ethyldiisopropylamine, flow 0.5 ml min^{-1}, (system 2) and gradient elution with 100% hexane 0 min; 1% acetone min^{-1} to 30%; 15 min; flow = 1.25 ml min^{-1} (system 3). Gas liquid chromatography (GLC) was carried out on a Varian 3700 instrument with a non-polar BP-1 capillary column (25 m × 0.25 mm) and a flame ionisation detector (FID), temperature program: 40°C 2 min; 10°C min^{-1} to 280°C; 10 min. 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.[27] Mass spectra were recorded on an AEI 902 spectrometer with a direct inlet to the ion source. IR spectra of solids were recorded in KBr discs and of liquids as a film between NaCl discs, on a Nicolet 20 SXC FT-IR spectrophotometer. CD spectra were recorded on a Jobin Yvon Auto Dicrograph Mark IV in EPA (diethyl ether–isopentane–ethanol 5:5:2) solution at room temperature. Optical rotation was measured on a Perkin Elmer 241 polarimeter. ^1H NMR, ^{13}C NMR and 2D ^1H–^1H correlated spectroscopy (COSY) were recorded on a 400 MHz (100 MHz for ^{13}C) Jeol EX400 instrument with $CDCl_3$ as solvent. Melting points of polyenes were recorded in evacuated tubes. All melting points are uncorrected.

*Synthesis of 2,7,11-trimethyl-12-oxo-2,4,6,8,10-tridecapentaenal (**3**).*

(2-E)-3-Methyl-2-penten-4-ynyl acetate (**6**). (2*E*)-3-Methyl-2-penten-4-yn-1-ol (**5**, 30 g, 0.31 mol) in dry benzene (135 ml) and dry pyridine (30 ml) was acetylated with acetyl chloride (27 g, 0.34 mol), as described by Samokhvalov *et al.*[14] The protected acetylenic alcohol **6** was isolated as a colourless oil in 77% yield (33.5 g, 0.24 mol), 99% pure (GLC), by distillation (72–74°C, ca. 20 mmHg). UV λ_{max} (CH_2Cl_2) 235 nm; IR (liq.) cm^{-1} 3290 s (C≡H), 3041–2930m (CH), 2098w (C≡C), 1742s (acetate), 1230s (acetate); MS [IP 70 eV, 150°C; *m/z* (% rel. int.)]: 138 (6, [*M*]), 123 (9, [*M* − 15]), 96 (17, [*M* − 42]), 95 (32, [*M* − 43]), 78 (17, [*M* − 60]), 43 (100); ^1H NMR ($CDCl_3$): δ 1.877 (s, 3 H, Me at C-3), 2.068 (s, 3 H, Me in AcO), 2.88 (s, 1 H, H-5), 4.64 (d, 2 H, *J* 7.3 Hz, H-1), 6.00 (t, 1 H, *J* 7.3 Hz, H-2).

(3E)-5-Acetoxy-3-methyl-3-penten-2-one (**7**). (2*E*)-3-Methyl-2-penten-4-ynyl acetate (**6**, 33.5 g, 0.24 mol) was treated with 90% aqueous acetic acid (170 ml) in the presence of mercuric sulfate (1.14 g, 3.85 mol) at 80–85°C as described by Samokhvalov *et al.*[14] The protected ketone **7** was isolated as a colourless oil in 45% yield (16.7 g, 0.11 mol), 98% pure (GLC), by distillation (106–112°C, ca. 20 mmHg). UV λ_{max} (CH_2Cl_2) 229 nm; IR (liq.) cm^{-1} 3062–2931s (CH), 1744s (acetate), 1675s (C=O), 1227s (acetate); MS [IP 70 eV, 150°C; *m/z* (% rel.int)]: 114 (9, [*M* − 42]), 96 (14, [*M* − 60]), 85 (28), 71 (8), 43 (100); ^1H NMR ($CDCl_3$): δ 1.811 (s, 3 H, Me at C-3), 2.113 (s, 3 H, Me in AcO), 2.344 (s, 3 H, Me-1), 4.82 (d, 2 H, *J* 5.9 Hz, H-5), 6.60 (*t*, 1 H, *J* 5.9 Hz, H-4).

(3E)-5-Hydroxy-3-methyl-3-penten-2-one (**8**). (i) Basic hydrolysis of (3*E*)-5-acetoxy-3-methyl-3-penten-2-one (**7**, 10 g, 0.064 mol) in methanol saturated with ammonia (60 ml) was carried out essentially according to Samokhvalov *et al.*[14] The reaction was monitored by TLC. Methanol and excess ammonia were evaporated off at reduced pressure. No further purification was necessary. The hydroxy ketone **8** was obtained as a colourless oil in 100% yield (7.3 g, 0.064 mol), 97% pure (GLC).

(ii) (2*E*)-3-Methyl-2-penten-4-yn-1-ol (**5**, 5.0 g, 0.052 mol) was dissolved in ethanol (10 ml) and water (0.9 ml, 0.05 mol). Hg–Nafion-H (500 mg) catalyst was added. The reaction mixture was stirred under an N_2 atmosphere at 20°C and monitored by TLC. After 75 h, the catalyst was filtered off and washed with ethanol followed by diethyl ether. The solvents were evaporated off at reduced pressure and water was removed by azeotropic distillation with benzene. No further purification of the product was necessary. The hydroxy ketone **8**, was obtained in 90% yield (5.36 g, 0.047 mol), 98% pure (GLC).

UV λ_{max} (CH_2Cl_2) 231 nm; IR (liq.) cm^{-1} 3404s (OH), 2970–2885s (CH), 1663s (C=O); MS [IP 70 eV, 150°C; *m/z* (% rel.int.)]: 114 (7, [*M*]), 96 (11, [*M* − 18]), 85 (36), 43 (100); ^1H NMR ($CDCl_3$): δ 1.767 (s, 3 H, Me at C-3), 2.343 (s, 3 H, Me-1), 4.44 (d, 2 H, *J* 5.4 Hz, H-5), 6.70 (t, 1 H, *J* 5.4 Hz, H-4).

(2E)-3-Methyl-4-oxo-2-pentenal (**4**). The above hydroxy ketone **8** (4.8 g, 0.043 mol) was dissolved in dry dichloro-

methane (200 ml). Manganese dioxide (48 g) was added and the reaction kept under an N_2 atmosphere at 20°C and monitored by TLC. The mixture was filtered after 30 h and the dichloromethane was evaporated off at 0°C and reduced pressure. The keto aldehyde **4** was isolated as a colourless oil in 21% yield (1.0 g, 8.9 mmol), 87% pure (GLC) by distillation (32–33°C, ca. 20 mmHg). Gas chromatography analysis of the crude product in dichloromethane prior to evaporation of the solvent indicated 100% pure **4**. When the solvent (CH_2Cl_2) was removed from the product at 0°C (reduced pressure) the product was found to co-evaporate, reducing the yield. Attempted removal of dichloromethane at atmospheric pressure was not successful since the keto aldehyde **4** decomposed when heated above 35°C.

When **4** was to be used in a subsequent Wittig reaction it was not isolated in a solvent-free state, but kept in dichloromethane under an N_2 atmosphere at −20°C until used. The keto aldehyde **4** was stable under these conditions for more than a year.

UV λ_{max} (CH_2Cl_2) 244 nm; MS [IP 30 eV, 130°C; *m/z* (% rel.int.)]: 112 (22, [*M*]), 88 (9, [*M* − 24]), 86 (47, [*M* − 26]), 84 (73, [*M* − 28]), 49 (100); ^{1}H NMR ($CDCl_3$): δ 2.244 (s, 3 H, Me at C-3), 2.417 (s, 3 H, Me-5), 6.61 (d, 1 H, *J* 7.3 Hz, H-2), 10.27 (d, 1 H, *J* 7.3 Hz, H-1).

*(All-*E*)-8-Hydroxy-2,7-dimethyl-2,4,6-octatrienal* (**11**). Partial reduction of 2,7-dimethyl-2,4,6-octatrienedial (**10**) was carried out essentially as described by Pattenden *et al.*[19] The C_{10}-dial (**10**, 20 g, 0.122 mol) and sodium borohydride (1.26 g, 0.03 mol) in ethanol (200 ml) afforded the hydroxy aldehyde **11** as a yellow viscous oil. CC followed by crystallisation from diethyl ether gave **11** as a light yellow semicrystalline powder in 80% yield (16.1 g, 0.097 mol), 97% pure (HPLC system 1 and TLC).

M.p. 58°C; UV–VIS λ_{max} (heptane) 295, 310, 323 nm, % III/II = 74; IR (KBr) cm^{-1} 3447s (OH), 3029–2848s (CH), 1653s (C = O), 1203s, 997m; MS [IP 70 eV, 150°C; *m/z* (% rel.int.)] 166 (93, [*M*]), 148 (42, [*M* − 18]), 137 (22), 135 (39), 108 (65, [*M* − 58]), 95 (100), 43 (90); ^{1}H NMR ($CDCl_3$): δ 1.870 (s, 3 H, Me at C-7), 1.880 (s, 3 H, Me at C-2), 4.17 (s, 2 H, H-8), 6.32 (d, 1 H, *J* 11.2 Hz, H-6), 6.66 (dd, 1 H, *J* 11.2 Hz, *J* 14.2 Hz, H-4), 6.93 (dd, 1 H, *J* 11.2 Hz, *J* 14.2 Hz, H-5), 6.95 (d, 1 H, *J* 11.2 Hz, H-3), 9.450 (s, 1 H, H-1).

*(All-*E*)-8-Chloro-2,7-dimethyl-2,4,6-octatrienal* (**12**). Chlorination of the hydroxy aldehyde **11** was carried out as described by Bernhard *et al.*[18] Treatment of **11** (0.8 g, 4.8 mmol) with conc. HCl (1.8 ml, 15.6 mmol) in dichloromethane (9 ml) followed by CC and crystallisation from diisopropyl ether gave **12** as light yellow crystals in 45% yield (0.4 g, 2.16 mmol).

M.p. 49–51°C; UV–VIS λ_{max} (CH_2Cl_2) 295, 318, 328 nm, % III/II = 45; IR (KBr) cm^{-1} 2989–2716m (CH), 1674s (C = O), 1607m, 1209m, 1180m, 994m, 964m (*trans* CH = CH); MS [IP 50 eV, 150°C; *m/z* (% rel. int.)] 186 (19, [*M*, ^{37}Cl]), 184 (61, [*M*, ^{35}Cl]), 151 (19), 150 (61), 149 (100), 148 (38), 135 (23), 121 (48), 119 (23), 108 (25), 107 (33), 106 (14), 105 (52), 95 (45), 93 (49), 91 (55), 43 (77); ^{1}H NMR ($CDCl_3$): δ 1.877 (s, 3 H, Me at C-2), 1.978 (s, 3 H, Me at C-7), 4.12 (s, 2 H, H-8), 6.32 (d, 1 H, *J* 10.7 Hz, H-6), 6.70 (dd, 1 H, *J* 11.2 Hz, *J* 14.6 Hz, H-4), 6.85 (dd, 1 H, *J* 11.2 Hz, *J* 14.6 Hz, H-5), 6.92 (d, 1 H, *J* 11.7 Hz, H-3), 9.470 (s, 1 H, H-1).

*(All-*E*)-(7-Formyl-2-methyl-2,4,6-octatrienyl)triphenylphosphonium chloride* (**9**). The phosphonium salt **9** was obtained as a light yellow powder in 26% yield (0.23 g, 0.51 mmol) from the above chloride **12** (0.36 g, 1.95 mmol) and triphenylphosphine (0.8 g, 3.1 mmol) in ethyl acetate (15 ml) as described by Bernhard *et al.*[18]

M.p. 232–233°C; UV–VIS λ_{max}(ethanol) 328 nm; IR (KBr) cm^{-1} 3037–2758m (CH), 1669s (C = O), 1603s, 1437m, 1113m, 691*m*; ^{1}H NMR ($CDCl_3$): δ 1.685 (s, 3 H, Me at C-2), 1.807 (s, 3 H, Me-8), 5.21 (d, 2 H, *J* 16.6 Hz, H-1), 6.22 (m, 1 H, H-3), 6.46 (m, 1 H, H-5), 6.66 (m, 1 H, H-4), 6.82 (d, 1 H, *J* 11.2 Hz, H-6), 7.64–7.99 (m, 15 H, aromatic H), 9.42 (s, 1 H, CHO).

*(All-*E*)-8-Bromo-2,7-dimethyl-2,4,6-octatrienal* (**13**). NBS (7.5 g, 42.1 mmol) was dissolved in dry dichloromethane (150 ml) and the solution was cooled to 0°C. Dimethyl sulfide (2.86 g, 3.4 ml, 46 mmol) was added dropwise under an N_2 atmosphere and with vigorous stirring. The reaction mixture was further cooled to −20°C and the hydroxy aldehyde **11** (5 g, 30.1 mmol) in dry dichloromethane (60 ml) was added dropwise with vigorous stirring. The mixture was kept at 20°C for 2.5 h and then poured over ice-cold brine and the product was extracted with diethyl ether. The ether phase was washed with half saturated sodium hydrogencarbonate followed by brine and finally water. The ether extract was dried over anhydrous sodium sulfate and solvents were removed at reduced pressure. The product was crystallised from diisopropyl ether in 86% yield (5.9 g, 25.9 mmol).

M.p. 63–64°C; UV–VIS λ_{max} (CH_2Cl_2) 326 nm; IR (KBr disc) cm^{-1} 2982–2720m (CH), 1670s (C = O), 1604s, 1204s, 1180m, 974m (*trans* CH = CH); MS [IP 50 eV, 150°C; *m/z* (% rel. int.)] 230 (17, [*M*, ^{81}Br]), 228 (17, [*M*, ^{79}Br]), 150 (67), 149 (100), 148 (27), 121 (45), 105 (46), 93 (55), 91 (62), 77 (49), 43 (26), 41 (48); ^{1}H NMR ($CDCl_3$): δ 1.876 (s, 3 H, Me at C-2), 2.008 (s, 3 H, Me at C-7), 4.07 (s, 2 H, H-8), 6.37 (d, 1 H, *J* 11.2 Hz, H-6), 6.71 (dd, 1 H, *J* 11.2 Hz, *J* 14.6 Hz, H-4), 6.83 (dd, 1 H, *J* 10.7 Hz, *J* 14.2 Hz, H-5), 6.92 (d, 1 H, *J* 11.2 Hz, H-3), 9.473 (s, 1 H, H-1).

*(All-*E*)-(7-Formyl-2-methyl-2,4,6-octatrienyl)triphenylphosphonium bromide* (**14**). The above bromide **13** (5.9 g, 25.7 mmol) was dissolved in ethyl acetate (150 ml). Triphenylphosphine (10.1 g, 38.6 mmol) was added and the reaction was kept at 20°C for 17 h. The product was filtered off, providing **14** as a yellow powder in 88% yield (10.8 g, 22.7 mmol).

M.p. 189°C; λ_{max}(ethanol) 328 nm; IR (KBr disc) cm^{-1} 3037–2713m (CH), 1668 s (C = O), 1602s, 1438s, 1111s, 690m; ^1H NMR ($CDCl_3$): δ 1.687 (s, 3 H, Me at C-2), 1.790 (s, 3 H, Me-8), 5.09 (d, 2 H, *J* 15.6 Hz, H-1), 6.20 (m, 1 H, H-3), 6.47 (m, 1 H, H-5), 6.66 (m, 1 H, H-4), 6.82 (d, 1 H, *J* 11.2 Hz, H-6), 7.62–7.95 (m, 15 H, aromatic H), 9.40 (s, 1 H, CHO).

*(All-*E*)-2,7,11-Trimethyl-12-oxo-2,4,6,8,10-tridecapentaenal* (**3**). (i) The above phosphonium salt **14** (1.5 g, 3.05 mmol) was dissolved in methanol (20 ml), trimethyl orthoformate (0.37 g, 0.38 ml, 3.5 mmol) and 1% *p*-toluenesulfonic acid in methanol (3 drops) was added at 35°C. The reaction mixture was kept at 30°C for 18 h, cooled to 0°C and ammonia-saturated methanol (5 drops) was added with vigorous stirring. After 30 min at 0°C, the solvents were evaporated off under reduced pressure. A ^1H NMR spectrum of the residue revealed a new singlet at 3.282 ppm integrating for 6 H. No signal was observed for an aldehyde proton. The protected phosphonium salt **21** was dissolved in dry dichloromethane (150 ml) and added together with the C_6-keto aldehyde **4** (estimated amount 0.34 g, 3.04 mmol) in dry dichloromethane, 20 ml) to a suspension of sodium hydride (0.22 g, unwashed) in dry dichloromethane (40 ml) under an N_2 atmosphere under conditions previously used for the synthesis of aleuriaxanthin.[28] The reaction mixture was kept at 20°C, under an N_2 atmosphere in the dark. TLC indicated that the reaction was finished after 20 h. The mixture was cooled to 0°C and 50% aqueous acetic acid (20 ml) was added. Half-saturated sodium hydrogencarbonate solution was added after 30 min and the product was extracted with dichloromethane. The organic phase was washed with water and dried over anhydrous sodium sulfate and the solvents were evaporated off under reduced pressure and the residue dissolved in benzene. The keto aldehyde **3** was isolated by CC as a red oil in 39% yield (0.293 g, 1.2 mmol) 100% pure (HPLC, system 3). HPLC (system 3) indicated 51% of all-*E*-**3** and 49% mono-*Z* isomers. Repeated crystallisation from acetone–hexane gave the crystalline all-*E*-**3** (54 mg) 100% pure (HPLC, system 3) as a bright red crystalline powder.

(ii) The above phosphonium salt **14** (2.0 g, 4.07 mmol) and the C_6-keto aldehyde **4** (estimated amount 0.46 g, 4.07 mmol) in dry dichloromethane, 27 ml) were added dropwise to a suspension of sodium hydride (0.3 g, unwashed) in dry dichloromethane (150 ml), at 20°C, under an N_2 atmosphere in the dark. The reaction was monitored by TLC. The reaction mixture was cooled to 0°C after 45 h and ice–water was added carefully and the product extracted with dichloromethane. The organic phase was washed with water, dried over anhydrous sodium sulfate and the solvents were removed under reduced pressure. The residue was dissolved in benzene and the C_{16}-keto aldehyde **3** was isolated by CC as a red oil in 43% yield (0.43 g, 1.76 mmol) 100% pure (HPLC, system 3). HPLC (system 3) indicated 71% of the all-*E* isomer and 29% mono-*Z* isomers. Repeated crystallisation from acetone–hexane yielded crystalline all-*E*-**3** (67 mg) 100% pure (HPLC, system 3) as a bright red crystalline powder.

M.p. 159–161°C; UV, VIS λ_{max} (hexane) 359, 378, 400 nm, % III/II = 88; IR (KBr) cm^{-1}, 3085–2860m (CH), 1716s (conjug. aldehyde, 1667s (conjug. ketone), 1362m, 1287w, 1233m, 973w (*trans* CH = CH); MS [IP 30 eV, 170°C; *m/z* (% rel.int.)]: 244 (98, [*M*]), 211 (16), 201 (15), 183 (15), 173 (17), 162 (17), 161 (26), 149 (28), 119 (33), 109 (32), 43 (100); ^1H NMR ($CDCl_3$): δ 1.907 (s, 3 H, Me at C-2), 1.959 (s, 3 H, Me at C-11), 2.067 (s, 3 H, Me at C-7), 2.378 (s, 3 H, Me-13), 6.43 (d, 1 H, *J* 11.7 Hz, H-6), ca. 6.70 (m, 2 H, H-8 and H-9), 6.78 (dd, 1 H, *J* 11.2 Hz, *J* 14.2 Hz, H-4), 6.98 (d, 1 H, *J* 14.1 Hz, H-3), 7.03 (dd, 1 H, *J* 11.7 Hz, *J* 14.2 Hz, H-5), 7.13 (d, 1 H, *J* 10.3 Hz, H-10), 9.48 (s, 1 H, H-1).

*Synthesis of sintaxanthin (***1***) and (3*R*)-3-hydroxysintaxanthin (***2***).*

*(1*E*)-1-(2,6,6-Trimethylcyclohex-1-enyl)-3-methyl-1,4-pentadien-3-ol* (**19**). (3*E*)-4-(2,6,6-Trimethylcyclohex-1-enyl)-but-3-en-2-one (**18**, 6.4 g, 33.0 mmol) was dissolved in dry THF (300 ml). The solution was cooled to 0°C and vinylmagnesium bromide in THF (50.0 mmol, 50 ml of a 1 M solution) was added dropwise with vigorous stirring under an N_2 atmosphere. The reaction mixture was kept at 20°C under N_2 for 20 h, cooled to 0°C and saturated aqueous ammonium chloride was added. The resulting mixture was kept at 0–20°C for 30 min. The product was extracted with diethyl ether and the organic phase was washed with ice-cold brine followed by water. Evaporation of the solvents at reduced pressure gave the allylic alcohol **19** as a yellow oil in 100% yield (7.24 g, 33.0 mmol) >95% pure (indicated by ^1H NMR and TLC).

UV–VIS λ_{max} (ethanol) 203, 226 nm; IR (liq.) cm^{-1} 3416s (OH), 2963–2827s (CH), 1456m, 1360m, 974m (*trans* CH = CH), 918m; MS [IP eV, 150°C; *m/z* (% rel.int.)] 220 (16, [*M*]), 202 (100, [*M* – 18]), 187 (55), 177 (45), 159 (47), 146 (61), 137 (56), 131 (82), 121 (53), 119 (62), 107 (55), 105 (63), 95 (51), 91 (74), 77 (49), 55 (59), 43 (95); ^1H NMR ($CDCl_3$): δ 0.971 (s, 6 H, ring-Me_2-6), 1.412 (s, 3 H, Me at C-3), 1.43 (m, 2 H ring-H-5), 1.59 (m, 2 H, ring-H-4), 1.648 (d, 3 H, *J* 1.0 Hz, ring-Me-2), 1.96 (m, 2 H, ring-H-3), 5.06 (dd, 1 H, *J* 1.5 Hz, *J* 10.3 Hz, H-5), 5.26 (dd, 1 H, *J* 1.5 Hz, *J* 17.6 Hz, H-5), 5.53 (d, 1 H, *J* 16.1 Hz, H-2), 6.00 (dd, 1 H, *J* 10.7 Hz, *J* 17.1 Hz, H-4), 6.07 (dd, 1 H, *J* 1.0 Hz, *J* 16.1 Hz, H-1).

*(All-*E*)-5-(2,6,6-Trimethylcyclohex-1-enyl)-3-methyl-2,4-pentadienylphosphonium bromide* (**17**). The phosphonium salt **17** was synthesised essentially according to the method reported by Loeber *et al.*[21] for **15**. The preceding allylic alcohol **19** (2.0 g, 9.1 mmol) was dissolved in methanol (100 ml). Triphenylphosphine hydrobromide (3.5 g, 10.2 mmol) was added and the reaction kept at

20 °C for 20 h. The solvent was evaporated off, water was added and the product extracted with dichloromethane. The organic phase was washed with water, dried over anhydrous sodium sulfate, concentrated and subjected to CC with ethyl acetate followed by methanol as the eluent. The methanol eluate was evaporated to dryness and the phosphonium salt **17** was obtained as a yellow crystalline powder in 73% yield (3.59 g, 6.6 mmol, ca. 85% pure (from ^{1}H NMR). The phosphonium salt **17** was used without further purification.

M.p. 92–98 °C; UV–VIS λ_{max}(methanol) 206, 222, 274 nm; IR (KBr) 3053–2862s (CH), 1586w, 1437s, 1189m, 1112s, 722s, 691s, 542s; ^{1}H NMR ($CDCl_3$): δ 0.939 (s, 6 H, ring-Me_2-6), 1.373 (d, 3 H, *J* 3.9 Hz, Me-3), 1.42 (m, 2 H, ring-H-5), 1.57 (m, 2 H, ring-H-4), 1.608 (s, 3 H, ring-Me-2), 1.96 (m, 2H, ring-H-3), 4.90 (dd, 2 H, *J* 7.8 Hz, *J* 15.6 Hz, H-1), 5.31 (dd, 1 H, *J* 6.8 Hz, *J* 14.2 Hz, H-2), 5.95 (m, 2 H, H-4 and H-5), 7.64–7.90 (m, 15 H, aromatic H).

*(1-*E*)-1-[(4*R*)-4-Hydroxy-2,6,6-trimethylcyclohex-1-enyl]-3-methyl-1,4-pentadien-3-ol* (**20**). The diol **20** was synthesised by a procedure similar to that used for **19**. 4-(4-Hydroxy-2,6,6-trimethylcyclohex-1-enyl)but-3-en-2-one (**16**, $[\alpha]_D^{20} = 73.4°$ (MeOH) consistent with reported data,[29] 2.20 g, 10.6 mmol) and vinylmagnesium bromide (29 mmol, 29 ml of a 1 M solution in THF) in dry THF (100 ml) afforded the diol **20** as a yellow oil in 100% yield (2.49 g, 10.6 mmol) >95% pure (indicated by ^{1}H NMR and TLC).

UV–VIS λ_{max} (ethanol) 203, 227 nm; IR (liq.) cm^{-1} 3363s (OH), 3087–2867s (CH), 1601w, 1454w, 1362m, 1045m, 975w (*trans* CH = CH), 920w; MS [IP 30 eV, 150 °C; *m/z* (% rel.int.)] 236 (16, [*M*]), 218 (8, [*M* – 18]), 203 (11), 175 (19), 159 (10), 147 (19), 145 (25), 135 (100), 121 (34), 119 (42), 109 (29), 107 (31), 105 (22), 95 (28), 84 (52), 43 (74); ^{1}H NMR ($CDCl_3$): δ 1.009 (s, 3 H, ring-Me-6), 1.024 (s, 3 H, ring-Me-6), 1.409 (s, 3 H, Me at C-3), 1.44 (m, 1 H, ring-H-5ax), 1.667 (s, 3 H, ring-Me-2), 1.74 (m, 1 H, ring-H-5eq), 1.99 (dd, 1 H, *J* 9.3 Hz, *J* 16.1 Hz, ring-H-3ax), 2.32 (dd, 1 H, *J* 5.9 Hz, *J* 16.6 Hz, ring-H-3eq), 3.97 (m, 1 H, ring-H-4), 5.07 (dd, 1 H, *J* 1.0 Hz, *J* 10.7 Hz, H-5), 5.25 (dd, 1 H, *J* 1.0 Hz, *J* 16.6 Hz, H-5), 5.53 (d, 1 H, *J* 16.1 Hz, H-2), 5.99 (dd, 1 H, *J* 10.7 Hz, *J* 17.1 Hz, H-4), 6.01 (d, 1 H, *J* 17.1 Hz, H-1).

*(All-*E*)-5-[(4*R*)-4-Hydroxy-2,6,6-trimethylcyclohex-1-enyl]-3-methyl-2,4-pentadienyltriphenylphosphonium bromide* (**15**). The phosphonium salt **15** was synthesised as described by Loeber *et al.*[21] The diol **20** (4.84 g, 20.5 mmol) and triphenylphosphine (8.0 g, 23.0 mmol) in methanol (240 ml) afforded, after work-up and CC as described for **17**, the hydroxylated phosphonium salt **15** as a yellow crystalline powder in 54% yield (6.23 g, 11.1 mmol) >95% pure (indicated by ^{1}H NMR).

M.p. 161–165 °C; UV λ_{max} (ethanol) 204, 223, 270 nm; IR (KBr) cm^{-1} 3276s (OH), 3054–2883s (CH), 1705w, 1586w, 1437s, 1111s, 744m, 722s, 691s; ^{1}H NMR ($CDCl_3$): δ 0.971 (s, 3 H, ring-Me-6), 0.986 (s, 3 H, ring-Me-6), 1.36 (d, 3 H, *J* 3.2 Hz, Me-3), 1.42 (m, 1 H, ring-H-5ax), 1.620 (s, 3 H, ring-Me-2), 1.73 (m, 1 H, ring-H-5eq), 1.99 (dd, 1 H, *J* 9.3 Hz, *J* 16.6 Hz, ring-H-3ax), 2.33 (dd, 1 H, *J* 5.4 Hz, *J* 17.1 Hz, ring-H-3eq), 3.95 (m, 1 H, ring-H-4), 5.02 (m, 2 H, H-1), 5.35 (dd, 1 H, *J* 6.8 Hz, *J* 14.2, H-2), 5.91 (s, 2 H, H-4 and H-5), 7.63–7.92 (m, 15 H, aromatic H).

*(All-*E*)-Sintaxanthin* (**1**). The phosphonium salt **17** (105 mg, 0.19 mmol) and the C_{16}-keto aldehyde **3** (30 mg, 0.12 mmol) were dissolved in dry dichloromethane (30 ml) and added dropwise to a suspension of sodium hydride (150 mg, unwashed) in dry dichloromethane (30 ml) under N_2 in the dark at 20 °C. The reaction was monitored by TLC. The reaction mixture was cooled to 0 °C after 48 h, ice–water was added carefully and the product extracted with dichloromethane. The organic phase was washed with water, dried over anhydrous sodium sulfate and the solvents were removed at reduced pressure. The red oily residue was dissolved in the minimum volume of benzene and subjected to CC. Sintaxanthin (**1**) was isolated in 76% yield (40 mg, 0.093 mmol) 100% pure (HPLC, system 2). HPLC (system 2) indicated a mixture of the all-*E* isomer (ca. 75%) and three different *Z* isomers (ca. 25%). Repeated crystallisation from methanol–diethyl ether gave the crystalline all-*E* sintaxanthin (**1**) as a red powder, 100% pure (HPLC, system 2).

M.p. 153 °C; VIS λ_{max} (acetone) 415, 447 ($E_{1\,cm}^{1\%}$ = 2340, ε = 105200) 464 nm; IR (KBr) cm^{-1} 3020–2822s (CH), 1646s (conj. ketone), 1610m, 1567w, 1524w, 1368w, 1324w, 1276m, 1237m, 1160w, 991w, 962s (*trans* CH = CH); MS [IP 70 eV, 190 °C; *m/z* (% rel. int.)]: 430 (82, [*M*]), 197 (10), 165 (10), 161 (16), 159 (12), 157 (12), 145 (17), 133 (16), 119 (35), 105 (34), 91 (32), 69 (49), 55 (39), 43 (100); ^{1}H NMR ($CDCl_3$): δ 1.030 (s, 6 H, Me-16 and Me-17), 1.46 (m, 2 H, H-2), 1.62 (m, 2 H, H-2), 1.719 (s, 3 H, Me-18), 1.939 (s, 3 H, Me-19′), 1.980 (s, 3 H, Me-19), 1.922 (s, 3 H, Me-20), 1.998 (s, 3 H, Me-20′), 2.04 (m, 2 H, H-4), 2.366 (s, 3 H, Me-7′), 6.13 (d, 1 H, *J* 16.0 Hz, H-8), 6.15 (d, 1 H, *J* 11.2 Hz, H-10), 6.20 (d, 1 H, *J* 16.0 Hz, H-7), 6.27 (d, 1 H, *J* 11.7 Hz, H-14), 6.36 (d, 1 H, *J* 15.6 Hz, H-12), 6.39 (d, 1 H, *J* 12.0 Hz, H-14′), 6.58 (dd, 1 H, *J* 10.7 Hz, *J* 15.1 Hz, H-11′), 6.63 (dd, 1 H, *J* 11.7 Hz, *J* 14.2 Hz, H-15′), 6.67 (d, 1 H, *J* 15.1 Hz, H-12′), 6.70 (dd, 1 H, *J* 11.7 Hz, *J* 15.1 Hz, H-11), 6.74 (dd, 1 H, *J* 11.2 Hz, 14.7 Hz, H-15), 7.14 (dd, 1 H, *J* 1.0 Hz, *J* 10.8 Hz, H-10′); ^{13}C NMR ($CDCl_3$): δ 11.7 (C-19′), 12.7–12.9 (C-19,20 and 20′), 19.2 (C-3), 21.8 (C-18), 25.6 (C-7′), 29.0 (C-16 and 17), 33.1 (C-4), 34.3 (C-1), 39.6 (C-2), 123.7 (C-11′), 126.0 (C-11), 127.0 (C-7), 129.3 (C-5), 129.6 (C-15), 130.7 (C-10), 132.0 (C-15′), 132.4 (C-14), 135.4 (C-14′), 135.5 (C-13′), 136.3 (C-9), 136.7 (C-13), 137.0 (C-9′), 137.7 (C-12), 137.9 (C-8), 138.2 (C-6), 140.0 (C-12′), 144.5 (C-10), 199.4 (C-8).

*(All-*E*)-(3*R*)-3-Hydroxysintaxanthin* (**2**). (All-*E*)-(3*R*)-hydroxysintaxanthin (**2**) was synthesised by the same procedure as for sintaxanthin (**1**). The phosphonium salt **15** (33.7 mg, 0.06 mmol) and the C_{16}-keto aldehyde **3** (15.0 mg, 0.06 mmol) treated with sodium hydride (50 mg, unwashed) in dichloromethane (2 × 20 ml) provided after 72 h, work-up as described for **1** and preparative TLC (system 1), 3-hydroxysintaxanthin (**2**) in 60% yield (15.9 mg, 0.036 mmol) 100% pure (HPLC, system 2). Excess C_{16}-keto aldehyde **3** (4.9 mg) was also isolated by TLC, indicating a 67% turnover of **15**. HPLC (system 2) indicated a mixture of all-*E*-**2** (73%) and two *Z* isomers (13 + 14%). Repeated crystallisation from methanol–diethyl ether gave (all-*E*)-(3*R*)-hydroxysintaxanthin (**2**) as a bright red crystalline powder, 100% pure (HPLC, system 2).

M.p. 193°C; VIS λ_{max} (acetone) 415, 448 ($E^{1\%}_{1\,cm}$ = 2363, ε = 105390), 468 nm; IR (KBr) cm^{-1}, 3410s (OH), 3021–2855s (CH), 1646s, (C = O), 1610w, 1325w, MS [IP 70 eV, 200°C; *m/z* (% rel.int.)]: 446 (100, [*M*]), 428 (3, [*M* − 18]), 197 (10), 161 (16), 157 (14), 145 (18), 119 (32), 105 (23), 91 (23), 43 (64), CD nm (Δε): 214 (0), 219 (− 0.5), 226 (0), 242 (+ 2.2), 258 (0), 279 (− 5.0), 330 (0), > 330 (+); ^{1}H NMR ($CDCl_3$): δ 1.075 (s, 3 H, Me-16 and Me-17), 1.48 (m, 1 H, H-2ax), 1.737 (s, 3 H, Me-18), 1.78 (m, 1 H, H-2eq), 1.937 (s, 3 H, Me-19′), 1.975 (s, 3 H, Me-19), 1.996 (s, 6 H, Me-20 and Me-20′), 2.06 (dd, 1 H, *J* 7.3 Hz, *J* 9.8 Hz, H-4ax), 2.366 (s, 3 H, Me-7′), 2.38 (dd, 1 H, *J* 2.4 Hz, *J* 6.4 Hz, H-eq), 4.00 (m, 1 H, H-3), 6.13 (s, 2 H, H-7 and H-8), 6.16 (d, 1 H, *J* 11.7 Hz, H-10), 6.27 (d, 1 H, *J* 11.2 Hz, H-14), 6.37 (d, 1 H, *J* 14.7 Hz, H-12), 6.39 (d 1 H, *J* 11.3 Hz, H-14′), 6.59 (dd, 1 H, *J* 10.3 Hz, *J* 14.6 Hz, H-11′), 6.64 (dd, 1 H, *J* 11.2 Hz, *J* 14.6 Hz, H-15′), 6.67 (d, 1 H, *J* 15.6 Hz, H-12′), 6.69 (dd, 1 H, *J* 10.7 Hz, *J* 15.2 Hz, H-11), 6.74 (dd, 1 H, *J* 11.2 Hz, *J* 14.2 Hz, H-15), 7.14 (dd, 1 H, *J* 1.0 Hz, *J* 10.8 Hz, H-10′); ^{13}C NMR ($CDCl_3$): δ 11.7 (C-19′), 12.7–12.9 (C-19, C-20 and C-20′), 21.6 (C-18), 25.7 (C-7′), 28.7 (C-16), 30.3 (C-17), 37.1 (C-1), 42.5 (C-4), 48.4 (C-2), 65.1 (C-3), 123.7 (C-11′), 125.8 (C-11), 126.0 (C-7), 126.5 (C-5), 129.4 (C-15), 132.1 (C-15′), 132.3 (C-10 and C-14), 135.5 (C-9), 135.6 (C-14′), 136.3 (C-13 and C-13′), 137.2 (C-9′), 137.7 (C-12), 138.0 (C-6), 138.4 (C-8), 140.0 (C-12′), 144.5 (C-10′), 199.4 (C-8′).

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