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Total Synthesis of C_{31}-Methyl Ketone Apocarotenoids 2:* The First Total Synthesis of (3*R*)-Triophaxanthin

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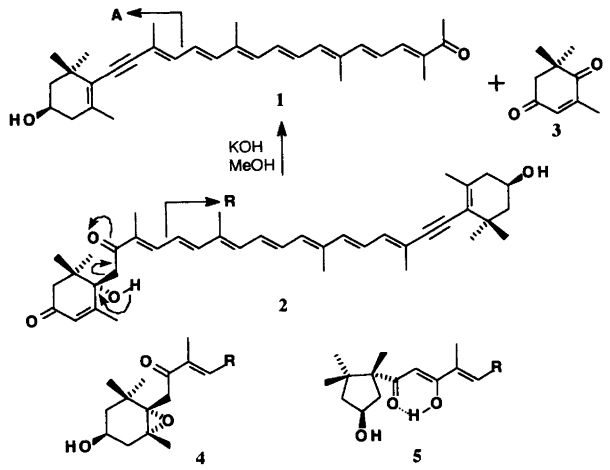
Five possible synthetic strategies have been developed for the synthesis of (all-*E*)-(3*R*)-triophaxanthin. A short discussion of these strategies is presented.

Fully characterised, optically active (all-*E*)-(3*R*)-triophaxanthin was prepared by total synthesis for the first time, with 9% overall yield, in 13 linear steps from the readily available (4*R*,6*R*)-actinol, (2*E*)-3-methyl-2-penten-4-yn-1-ol, (all-*E*)-2,7-dimethyl-2,4,6-octatrienedial and 1,1-dimethoxypropanone.

Triophaxanthin (**1**), see Scheme 1, is one of two known naturally occurring acetylenic C_{31}-methyl ketone apocarotenoids.[1] The first isolation and the structural elucidation of **1** was reported by McBeth in 1972.[2] Triophaxanthin (**1**) is a marine pigment and was isolated as the major carotenoid, constituting more than 52% of the total pigment, from the nudibranch *Triopha carpentieri*.[2] Furthermore, **1** has been isolated as a major pigment in three different bryozoans known to be included in the diet of *T. carpentieri*, and is believed to be resorbed unchanged from the food source.[2] Triophaxanthin (**1**) has also been identified as a minor carotenoid in the mollusc *Loligo vulgaris*.[3]

Matsuno *et al.*[4] demonstrated that treatment of the marine acetylenic C_{40}-carotenoid amarouciaxanthin B (**2**) with methanolic potassium hydroxide resulted in formation of triophaxanthin (**1**) and 6-oxoisophorone (**3**), presumably via a retro aldol cleavage as depicted in Scheme 1. Amarouciaxanthin B (**2**), as well as the marine carotenoids halocynthiaxanthin (**4**) and mytiloxanthin (**5**), constitute possible metabolic precursors for triophaxanthin (**1**).



Scheme 1.

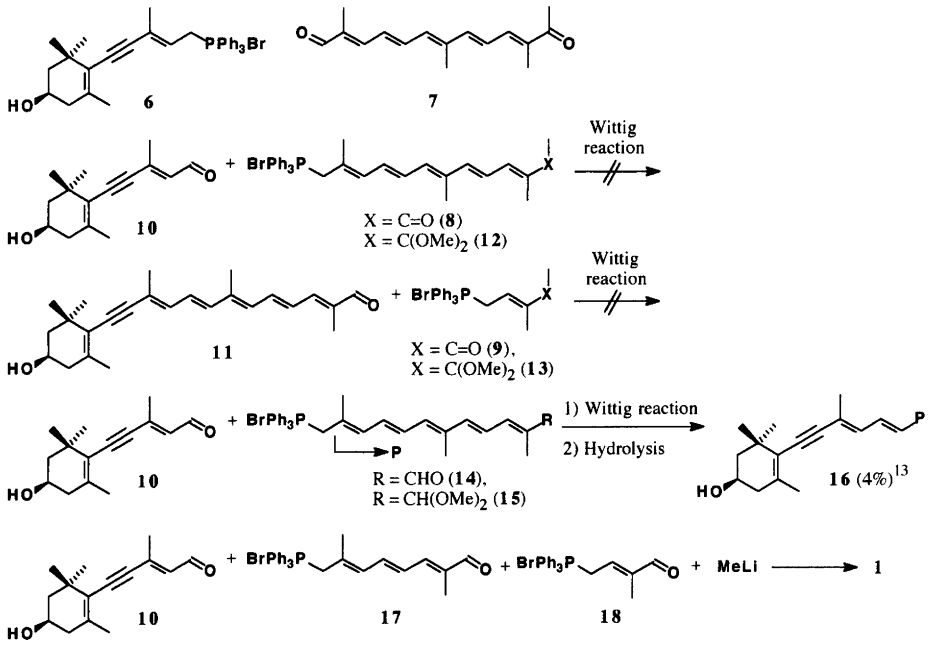
In this paper the first total synthesis of optically active (3*R*)-triophaxanthin (**1**) is reported. The configuration at the single stereogenic center of naturally occurring **1** is unknown. However, in all carotenoids containing end group **A**, see Scheme 1, for which the absolute stereochemistry is known, the 3*R*-isomer is the naturally occurring stereoisomer, cf. Straub[1] and references therein. Thus, the 3*R*-isomer of **1** was the target compound in the present synthesis.

Results and discussion

The synthetic strategy. Five different synthetic strategies were considered for the total synthesis of (3*R*)-triophaxanthin (**1**), see Scheme 2. The $C_{15}+C_{16}$ strategy employed for the synthesis of the sintaxanthins,[5] required the use of the acetylenic C_{15}-phosphonium salt **6** and the C_{16}-keto aldehyde **7**. Weedon and co-workers[6] first prepared **6** for the synthesis of mytiloxanthin (**5**). However, it has been demonstrated that acetylenic phosphonium salts like **6**[6,7] and its 4-oxo analogues,[8,9] predominantly provide the thermodynamically favored[10] 9*Z* isomeric Wittig condensation products. Since the all-*E* isomer of **1** was the target compound in the present work, this strategy was abandoned.

The alternative $C_{15}+C_{16}$ and the $C_{25}+C_6$ strategy depicted in Scheme 2 required the preparation of the

* For Part 1, see *Acta Chem. Scand. 48* (1994) 657.



Scheme 2.

novel C_{16}- and C_6-phosphonium salts **8** and **9**, respectively. The synthesis of the acetylenic C_{15}-and C_{25}-hydroxy aldehydes **10** and **11**, employed in the synthesis of diatoxanthin, has recently been reported.[11,12] The C_{16}-phosphonium salt **8** has been prepared in 43% yield over three steps from the C_{16}-keto aldehyde **7** and the C_6-phosphonium salt **9** in 12% yield over three steps from the commercially available (2*E*)-3-methyl-2-penten-4-yn-1-ol.[13] Neither of the phosphonium salts **8** or **9** could be converted into the corresponding ylides, unless the keto moieties were protected. Thus, **8** or **9** were converted into the corresponding dimethyl ketals **12** and **13**. The blue ylide formed from **12** was surprisingly stable, as demonstrated by no or insignificant loss in color intensity when a solution of the ylide in methanolic potassium hydroxide was stirred under an atmosphere of air for more than 4 h.[13] The phosphonium salts **12** and **13** did not undergo the desired Wittig reactions, with the aldehydes **10** or **11** respectively, at room temperature.[13] The strategies based upon the use of methyl ketone phosphonium salts were consequently discontinued.

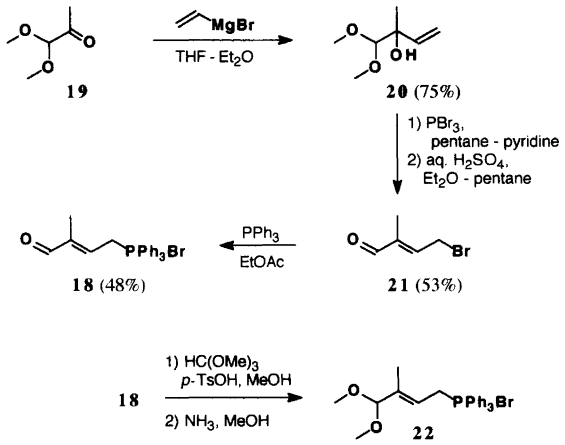
The carbon backbone of triophaxanthin (**1**) may be constructed by addition of methyllithium to the aldehyde moiety of an appropriate C_{30}-apocarotenal. This strategy has previously been employed for the first synthesis of sintaxanthin.[14] The novel C_{15}-phosphonium salt **14** was prepared, in ca. 16% yield over six steps from (all-*E*)-2,7-dimethyl-2,4,6-octatrienedial,[13] for the synthesis of the key intermediate acetylenic C_{30}-hydroxy aldehyde **16**. Protection of the aldehyde moiety was necessary in order to allow ylide formation from **14**. However, the Wittig reaction of the dimethyl acetal protected phosphonium salt **15** with the acetylenic C_{15}-hydroxy aldehyde **10**, followed by hydrolysis of the acetal, provided an unsatisfactory 4% yield of **16**.[13]

Finally, a strategy utilising the key intermediate acetylenic C_{30}-hydroxy aldehyde **16**, prepared according to a highly convergent $C_{15}+C_{10}+C_5$ approach from the acetylenic C_{15}-hydroxy aldehyde **10** and the C_{10}- and C_5-phosphonium salts **17** and **18**, proved successful for the synthesis of (3*R*)-triophaxanthin (**1**). A detailed account of these results is given in the present work. Preliminary results have been reported.[15]

The $C_{15}+C_{10}+C_5+C_1$ approach, originally elaborated for the present synthesis of (3*R*)-triophaxanthin (**1**),[15] was recently employed for the first syntheses of (3*S*)-7′-apohopkinsiaxanthin[15,16] and (3*S*,5*R*,6*R*)-paracentrone.[17,18]

Synthesis of the C_5-phosphonium salt **18**. The C_5-oxo phosphonium salt **18** was prepared essentially according to a method reported by Brown and Weedon,[19] see Scheme 3. A Grignard reaction between the commercially available C_3-ketone **19** and vinylmagnesium bromide afforded the tertiary allylic C_5-alcohol **20** in 75% yield. Bromination of **20** with phosphorus tribromide followed by hydrolysis of the dimethyl acetal, gave a 53% yield of the C_5-bromide **21**. Treatment of **21** with triphenylphosphine in ethyl acetate finally furnished the desired phosphonium salt **18** in 48% yield, or 19% overall yield from **19**. Direct conversion of the alcohol **20** into **18** by treatment of the former with triphenylphosphine hydrobromide in chloroform was unsuccessful.

Protection of the aldehyde moiety was required in order to convert the C_5-phosphonium salt **18** into the corresponding ylide. The diethyl acetal protected C_5-phosphonium salt may be prepared directly from the diethyl acetal analogue of **20**, as previously demonstrated by Brown and Weedon.[19] However, dialkyl acetal pro-



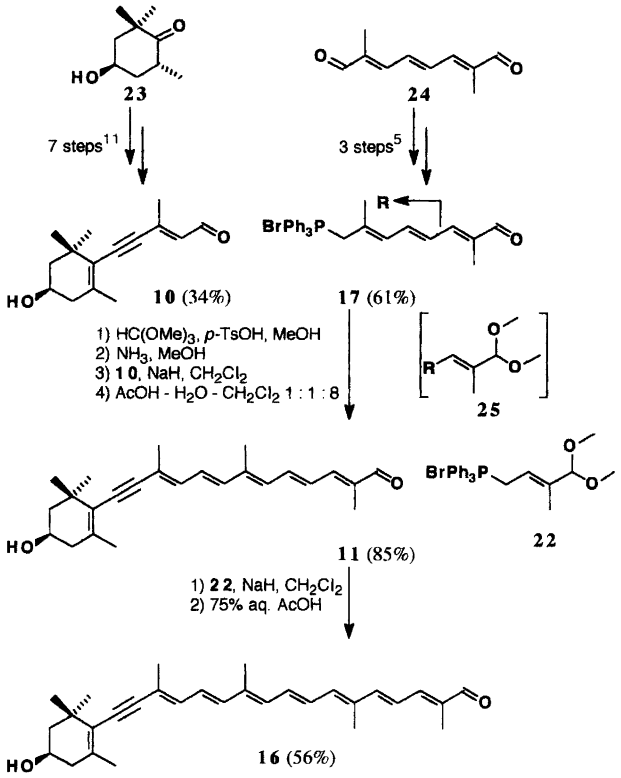
Scheme 3.

tected phosphonium salts are hygroscopic and more difficult to crystallise than the free oxo analogues.[19] Here, the oxo phosphonium salt **18** was prepared and converted into the dimethyl acetal phosphonium salt **22**, upon treatment with trimethyl orthoformate in the presence of catalytic amounts of *p*-toluenesulfonic acid followed by neutralisation with ammonia, just prior to use in the Wittig reaction.

Synthesis of (3R)-triophaxanthin (**1**). The acetylenic C_{25}-hydroxy aldehyde **11** was, as already briefly mentioned, prepared in connection with the synthesis of diatoxanthin. A $C_{15}+C_{10}$ approach, based on the acetylenic C_{15}-hydroxy aldehyde **10** and the C_{10}-oxo phosphonium salt **17**, was employed.[12] The aldehyde **10**, prepared[11] in 34% overall yield from (4*R*,6*R*)-actinol (**23**, cf. Scheme 4), was coupled directly with the C_{10}-phosphonium salt **17**, first prepared[5] in 61% overall yield from the symmetrical C_{10}-dial **24** for the synthesis of the sintaxanthins. One equivalent of **17** was employed. Incomplete conversion of the aldehyde **10** resulted in a crude mixture containing unreacted substrate and the condensation product **11**. Separation of the C_{15}-and C_{25}-aldehydes **10** and **11** proved exceedingly difficult. As a result, the pure C_{25}-aldehyde **11** was obtained in low (40%) yield after chromatographic isolation.[12]

In the present work, an improved yield of the C_{25}-aldehyde **11** was obtained by carrying out the $C_{15}+C_{10}$ Wittig condensation with an excess of the dimethyl acetal protected C_{10}-phosphonium salt **25**, prepared by treatment of **17** with trimethyl orthoformate in acidic methanol followed by neutralisation. Complete conversion of **10** was obtained within 17 h. Acidic hydrolysis of the dimethyl acetal functionality gave the acetylenic C_{25}-hydroxy aldehyde **11** in 85% yield, as a mixture of the all-*E* isomer, constituting 66% of total **11**, and three *Z* isomers.

A Wittig reaction between the C_5-phosphonium salt **22** and the *E*/*Z* isomeric mixture of the C_{25}-hydroxy aldehyde **11**, followed by acidic hydrolysis of the dimethyl acetal, furnished the acetylenic C_{30}-hydroxy aldehyde **16**

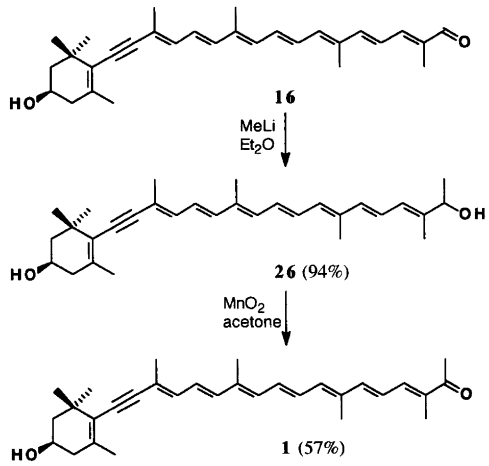


Scheme 4.

in 56% yield. The product was obtained as a mixture of the all-*E* isomer, constituting 70% of total **16**, and two *Z* isomers. Pure all-*E*–**16** was obtained by crystallisation from benzene. The isomeric mixture was employed in the subsequent step. Treatment of the acetylenic C_{30}-hydroxy aldehyde **16** with methyllithium in diethyl ether afforded the acetylenic C_{31}-dihydroxy aldehyde **26** in 94% yield, see Scheme 5. A 4:1 mixture of the two C-8′ epimeric diols containing ca. 67% of the all-*E* isomers, as demonstrated by ^{1}H NMR spectroscopy, was obtained.

The result of the oxidation of the secondary allylic hydroxy group in **26** proved surprisingly solvent dependent. Oxidation of **26** with manganese dioxide in dichloromethane gave complete conversion of the substrate in less than 15 min. (3*R*)-Triophaxanthin (**1**) was identified as one of three major products in a complex mixture. Yokoyama and White[14] have carried out the allylic manganese dioxide oxidation of 8′-hydroxy-7′-apo-β-carotene with acetone as the solvent, giving sintaxanthin in 75% yield. The reported reaction time was 6 h. In a similar fashion, allylic oxidation of **26** with manganese dioxide in acetone, provided (3*R*)-triophaxanthin (**1**) 57% yield. Complete conversion of **26** was observed after 1 h. HPLC of the column chromatography purified product indicated a mixture of the all-*E* isomer, constituting 67% of total **1**, and three *Z* isomers. Recrystallisation from benzene furnished pure (all-*E*)-(3*R*)-triophaxanthin (**1**).

The overall yield of (3*R*)-triophaxanthin (**1**) was 9%



Scheme 5.

over 13 linear steps, or a total of 22 steps, starting from (4*R*,6*R*)-actinol (**23**). All spectral data (UV–VIS, IR, MS, ^{1}H NMR, ^{13}C NMR and CD) for the synthetic compound were as expected for **1**, and in accordance with data reported[2] for the natural compound. The CD spectrum of **1** was typically non-conservative, with relatively weak Cotton effects and only one sign shift, as expected for carotenoids containing a chiral acetylenic 3-hydroxy-β-end group.[20,21] More intense Cotton effects were reported for a semisynthetic sample of **1**,[4] presumably due to contaminants in the latter sample. The optical properties confirmed the 3*R*-configuration for synthetic triophaxanthin (**1**) by comparison of the present data for **1** with those previously reported for the monoacetylenic (all-*E*)-(3*R*)-7,8-didehydrocryptoxanthin[12] and the diacetylenic (all-*E*)-(3*R*,3′*R*)-alloxanthin.[21,22]

Reisolation of **1** would need to be carried out for comparison of optical data for natural and synthetic triophaxanthin (**1**), in order to determine the absolute configuration of the naturally occurring compound.

Experimental

General methods. Solvents were of distilled or *p.a.* quality. Diethyl ether used for extraction was chromatographed through alumina (neutral). Diethyl ether and THF used as solvents in reactions were distilled from sodium–benzophenone. Pyridine was distilled from solid potassium hydroxide. Dichloromethane, hexane, pentane, methanol and DMF were dried over freshly activated 3 Å molecular sieves before being employed as solvents in reactions. Sodium hydride was washed with hexane followed by dichloromethane before use. Solvents were evaporated from reaction mixtures at reduced pressure (ca. 20 mmHg) at temperatures not exceeding 35 °C. Kugelrohr distillation was performed with a Büchi GKR-51 apparatus. Melting points of polyenes were recorded in evacuated tubes. All melting points are uncorrected.

Chromatography. Analytical thin layer chromatography (TLC) was performed on precoated Silica gel 60 F_{254} (Merck Art. 5554) plates with ethyl acetate–heptane 2:3 (system 1) or 1:1 (system 2) as the eluent. Methanolic sulfuric acid (30%) was used for developing TLC plates to detect the presence of non-UV active compounds. Preparative TLC was performed on silica gel 60 G (Merck Art. 7731) with ethyl acetate–heptane 2:3 (system 1) or 1:1 (system 2) as the eluent. Column chromatography (CC) was performed on silica gel 60 (Merck Art. 7734) with mixtures of ethyl acetate in hexane as the eluent. High performance liquid chromatography (HPLC) was carried out on a Hewlett Packard series 1050 instrument on a Techsphere 5 CN nitrile column with gradient elution starting at 100% hexane 0 min; 1% acetone min^{-1} to 30%; 15 min, flow = 1.25 ml min^{-1} (system 1), or on a Spherisorb S5W silica column with methanol–dichloromethane 1:19 as the eluent, flow = 0.25 ml min^{-1} (system 2). For analysis of colored compounds, the diode array (DA) detector was set to detect at five different wavelengths simultaneously (330, 360, 390, 420, 450 nm). For analysis of colorless compounds the detector was set to the wavelength relevant for the compound in question, as determined by UV spectroscopy. Gas liquid chromatography (GLC) was performed on a Varian 3700 instrument with a non-polar BP-1 capillary column (25 m × 0.25 mm) and a flame ionisation detector (FID). The split ratio was 1:9; temperature program: 40 °C 2 min; 10 °C min^{-1} to 280 °C; 10 min.

Spectroscopy. UV–VIS spectra were recorded on a Perkin Elmer 552 spectrophotometer. Spectral fine structure was measured as %III/II.[23] Solvents are specified in each case. IR spectra of solids were recorded for KBr discs and of liquids as a film between NaCl discs, on a Nicolet 20 SXC FT-IR spectrophotometer. Mass spectra were recorded on an AEI 902 spectrometer with a direct inlet to the ion source. Temperature and ionisation potential are specified in each case. 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. ^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY spectra were recorded on a 300 MHz (75 MHz for ^{13}C) Bruker Avance DPX300 or 400 MHz (100 MHz for ^{13}C) Jeol EX400 instrument with $CDCl_3$ as the solvent. Standard Bruker or Jeol software was used.

(2RS)-1,1-Dimethoxy-2-methyl-3-buten-2-ol (**20**). The precursor 1,1-dimethoxypropanone (**19**, 11.20 g, 94.91 mmol) was dissolved in dry diethyl ether (150 ml) and the resulting solution was cooled to 0 °C under an N_2 atmosphere. Vinylmagnesium bromide (100.00 mmol, 100 ml of a 1.0 M solution in THF) was added dropwise over 30 min. The reaction mixture was stirred at 20 °C under N_2 for 16 h and cooled to 0 °C. Saturated aqueous ammonium chloride (300 ml) was added and the mixture

was stirred for 1 h. The product was extracted with diethyl ether. The ether phase was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvents gave a yellow oil which, after purification by kugelrohr distillation at 70 °C (ca. 20 mmHg), afforded the alcohol **20** as a colorless oil in 75% yield (10.41 g, 71.30 mmol), 97% pure (GLC). GLC $t_R = 6.3$ min; IR (liq.) cm^{-1}: 3472s (OH), 3090–2835s (CH), 1451 m, 1413w, 1372 m, 1321w, 1186s, 1105s, 1079s, 982 m, 923 m, 692w; MS [IP 15 eV, 150 °C: *m/z* (% rel. int.)] 115 (2, [*M*−31]), 83 (4), 75 (100, [possibly MeO^+=CH–OMe]), 48 (8); ^1H NMR ($CDCl_3$): δ 1.255 (s, 3 H, Me at C-2), 3.529 (s, 3 H, MeO), 3.548 (s, 3 H, MeO), 4.044 (s, 1 H, H-1), 5.16 (dd, 1 H, $J_{4,4}$ 1.5 Hz, $J_{3,4\text{-}cis}$ 10.7 Hz, H-4), 5.36 (dd, 1 H, $J_{4,4}$ 1.5 Hz, $J_{3,4\text{-}trans}$ 17.6 Hz, H-4), 6.00 (dd, 1 H, $J_{3,4\text{-}cis}$ 10.7 Hz, $J_{3,4\text{-}trans}$ 17.1 Hz, H-3).

(2E)-4-Bromo-2-methyl-2-butenal (**21**). A solution of the preceding alcohol **20** (2.70 g, 18.49 mmol) in dry pentane (15 ml) and dry pyridine (2.5 ml) was cooled to −20 °C under N_2. Phosphorus tribromide (4.20 g, 15.56 mmol) in dry pentane (5 ml) was added dropwise over 30 min. The reaction mixture was stirred at 20 °C for 3 h and subsequently poured into sulfuric acid (1 M, 100 ml) at 0 °C. Diethyl ether (100 ml) was added and the reaction mixture was stirred at 0 °C in the dark for 3 h. The two phases were separated and the water phase was extracted with diethyl ether. The combined organic phase was washed with saturated aqueous sodium hydrogen carbonate, water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvents gave the bromide **21** as a light yellow oil in 53% yield (1.60 g, 9.81 mmol), >75% pure. UV–VIS: λ_{max}(diethyl ether) 228; MS [IP 30 eV, 140 °C: *m/z* (% rel. int.)] 164 (7, [*M*, ^{81}Br]), 162 (6, [*M*, ^{79}Br]), 83 (29), 75 (100), 55 (42), 43 (13); ^1H NMR ($CDCl_3$): δ 1.815 (s, 3 H, Me at C-2), 4.15 (d, 2 H, $J_{3,4}$ 8.3 Hz), 6.64 (tq, 1 H, $J_{Me,H\text{-}3}$ 1.5 Hz, $J_{3,4}$ 8.3 Hz, H-3), 9.468 (s, 1 H, H-1).

(2E)-(3-Methyl-4-oxo-2-butenyl) triphenylphosphonium bromide (**18**). (i) To a solution of the preceding alcohol **20** (1.00 g, 6.85 mmol) in chloroform (15 ml) was added triphenylphosphonium hydrobromide (2.50 g, 7.29 mmol). The reaction mixture was stirred at 20 °C for 28 h, cold saturated aqueous sodium hydrogen carbonate was added and the phases were separated. The water phase was extracted with chloroform, the combined organic phase was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded an orange viscous oil. The ^1H NMR of the product indicated the presence of several products, but no product with any olefinic protons.

(ii) The preceding bromide **21** (0.85 g, 5.21 mmol) was dissolved in dry ethyl acetate (60 ml) and triphenylphosphine (2.30 g, 7.77 mmol) was added. The reaction mixture was stirred at 20 °C under N_2 in the dark for 20 h. The precipitate that formed during the reaction was filtered off and washed thoroughly with ethyl acetate and dried at 20 °C under reduced pressure (0.01 mmHg) for 5 h, affording the phosphonium salt **18** as a white solid in 48% yield (1.07 g, 2.52 mmol), >95% pure (^1H NMR). M.p. 254–260 °C; UV–VIS: λ_{max}(ethanol) 206, 212, 298 nm; ^1H NMR ($CDCl_3$): δ 1.42 (dd, 3 H, $J_{Me,H\text{-}2}$ 1.5 Hz, $J_{Me,P}$ 4.0 Hz, Me at C-3), 5.38 (dd, 2 H, $J_{H\text{-}1,P}$ 16.6 Hz, $J_{1,2}$ 7.8 Hz, H-1), 6.54 (dtq, 1 H, $J_{Me,H\text{-}2} \approx 1$ Hz, $J_{1,2} \approx 8$ Hz, $J_{H\text{-}2,P} \approx 9$ Hz, H-2), 7.67–7.97 (m, 15 H, aromatic H), 9.358 (s, 1 H, H-4).

(all-E)-(3R)-3-Hydroxy-7,8-didehydro-12'-apo-β-carotenal (**11**). The available[5] C_{10}-phosphonium salt **17** (1.00 g, 2.04 mmol) was dissolved in dry methanol (10 ml) and the solution was heated to 30–35 °C. *p*-Toluenesulfonic acid (3 drops of a 1% solution in methanol) and trimethyl orthoformate (0.25 ml, 2.25 mmol) were added and the reaction mixture was stirred at 30–35 °C in the dark for 20 h and then cooled to 0 °C. Ammonia (5 drops of a saturated solution in methanol) was added and the reaction mixture was stirred at 0 °C for 30 min. The solvent was evaporated off and the resulting residue was heated at 30 °C under reduced pressure (0.01 mmHg) to remove excess formate, ammonia and methanol, yielding the protected C_{10}-phosphonium salt **25** as a yellow solid. UV–VIS: λ_{max}(-methanol) 204, 222, 274, 289, 303 nm; ^1H NMR ($CDCl_3$): δ 1.57 (dd, 3 H, $J_{Me,H\text{-}3} \approx 1$ Hz, $J_{Me,P}$ 4.4 Hz, Me at C-2), 1.66 (s, 3 H, Me at C-7), 3.25 (s, 6 H, MeO), 4.51 (s, 1 H, H-8), 4.76 (d, 2 H, $J_{H\text{-}1,P}$ 15.8 Hz, H-1), 5.7–6.3 (m, 4 H, olefinic protons), 7.6–7.9 (m, 15 H, aromatic H).

A solution of the protected C_{10}-phosphonium salt **25** and the available[11] C_{15}-hydroxy aldehyde **10** (0.35 g, 1.51 mmol) in dry dichloromethane (30 ml) was added dropwise to a stirred suspension of sodium hydride (0.40 g, unwashed) in dry dichloromethane (50 ml) at 20 °C under N_2 in the dark. The reaction was monitored by TLC (system 1) and UV–VIS spectroscopy. TLC indicated complete conversion of **10** after 17 h. The reaction mixture was cooled to 0 °C and an ice-cold 1:1 mixture of acetic acid–water (20 ml) was added dropwise with vigorous stirring. After 30 min at 0 °C, water was added and the product was extracted with dichloromethane. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and the solvent was evaporated off to yield a red oily residue. CC afforded the C_{25}-hydroxy aldehyde **11** as a red oil in 85% yield (0.47 g, 1.29 mmol), >99% pure [TLC (system 1), HPLC (system 1)]. HPLC (system 1) indicated a mixture of the all-*E* isomer (66%) and three *Z* isomers (2+19+13%). No attempt was made to isolate the all-*E* isomer. The isomeric mixture was employed in the spectroscopic analysis and in the following Wittig reaction. ^1H NMR assignments are given for the all-*E* isomer only. HPLC (system 1) $t_R = 17.8$ min; UV–VIS: λ_{max}(hexane) 410 nm, λ_{max}(acetone) 413 nm, λ_{max} [HPLC eluent (all-*E* isomer)] 417 nm; MS [IP 70 eV, 200 °C: *m/z* (%

rel. int.)] 364 (64, [*M*]), 346 (4, [*M*−18]), 249 (17), 247 (11), 237 (11), 211 (14), 207 (17), 197 (20), 195 (19), 179 (16), 165 (20), 157 (20), 143 (18), 129 (21), 119 (21), 115 (23), 105 (29), 95 (23), 91 (42), 55 (48), 43 (100); ^{1}H NMR ($CDCl_3$): δ 1.154 (s, 3 H, Me-16), 1.209 (s, 3 H, Me-17), 1.45 (m, 1 H, H-2_{ax}), 1.84 (m, 1 H, H-2_{eq}), 1.89 (s, 3 H, Me-20′), 1.93 (s, 3 H, Me-18), 2.03 (s, 6 H, Me-19 and Me-20), 2.07 (m, 1 H, H-4_{ax}), 2.44 (dd, 1 H, *J* 5.4 Hz, *J* 17.5 Hz, H-4_{eq}), 3.99 (m, 1 H, H-3), 6.32 (d, 1 H, $J_{14,15}$ 11.6 Hz, H-14), 6.37 (d, 1 H, $J_{11,12}$ 15.1 Hz, H-12), 6.46 (dq, 1 H, $J_{Me\text{-}19,H\text{-}10}$ 1.2 Hz, $J_{10,11}$ 11.9 Hz, H-10), 6.67 (dd, 1 H, $J_{10,11}$ 11.9 Hz, $J_{11,12}$ 14.9 Hz, H-11), 6.71 (dd, 1 H, $J_{14',15'}$ 11.7 Hz, $J_{15,15'}$ 14.5 Hz, H-15′), 6.97 (d, 1 H, $J_{14',15'}$ 11.4 Hz, H-14′), 7.03 (dd, 1 H, $J_{14,15}$ 11.7 Hz, $J_{15,15'}$ 14.3 Hz, H-15), 9.467 (s, 1 H, H-12′).

*(all-*E*)-(3*R*)-3-Hydroxy-7,8-didehydro-8′-apo-β-carotenal* (**16**). The protected C_5-phosphonium salt **22** was prepared from the C_5-phosphonium salt **18** (1.05 g, 2.47 mmol) in methanol (10 ml) with *p*-toluenesulfonic acid (5 drops of a 1% solution in methanol) and trimethyl orthoformate (0.31 ml, 2.80 mmol) at 30–35 °C followed by neutralisation with ammonia (5 drops of a saturated solution in methanol) at 0 °C, as described for the protection of the aldehyde moiety of the corresponding C_{10}-phosphonium salt **17**. The C_{25}-hydroxy aldehyde **11** (0.44 g, 1.20 mmol) and **22** in dry dichloromethane (30 ml) were added dropwise to a stirred suspension of sodium hydride (0.60 g, unwashed) in dry dichloromethane (50 ml) at 20 °C under N_2 in the dark. The reaction was monitored by TLC (system 1) and UV–VIS spectroscopy. Complete conversion of the C_{25}-hydroxy aldehyde **11** was observed after 45 h. The reaction mixture was cooled to 0 °C, ice–water was added dropwise to decompose the excess sodium hydride and the product was extracted with dichloromethane. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and evaporated to dryness. The red oily residue was subjected to CC, providing 0.35 g of a ca. 1:2 mixture of the C_{30}-aldehyde **16** and the corresponding dimethyl acetal protected aldehyde, as demonstrated by ^{1}H NMR spectroscopy. The product mixture was stirred in 75% aqueous acetic acid (90 ml) at 20 °C under N_2 in the dark for 45 min. The reaction mixture was cooled to 0 °C and 15% aqueous sodium hydroxide was added with vigorous stirring until pH ≈ 7. The product was extracted with diethyl ether. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and evaporated to dryness. CC of the residue provided the C_{30}-hydroxy aldehyde **16** as a red solid in 56% yield (0.29 g, 0.67 mmol) from **11**, >99% pure [TLC (system 1), HPLC (system1)]. HPLC (system 1) indicated a mixture of the all-*E* isomer (70%) and two *Z* isomers (13+17%). The all-*E* isomer crystallised from an aliquot in benzene as a violet crystalline powder, ca. 96% pure [HPLC (system 1), ^{1}H NMR], containing ca. 4% benzene after 8 h at 20 °C under reduced pressure (0.01 mmHg). M.p. 175–177 °C (evacuated tube); TLC (system 2) R_f = 0.48; HPLC (system 1) t_R = 17.8 min; UV–VIS: λ_{max}(hexane) 420, 447, 475 nm, %III/II = 14, λ_{max}(acetone) 420, 447 ($E^{1\%}_{1\,cm}$ = 2180, ε = 93800, corrected for 4% benzene in the crystalline sample: $E^{1\%}_{1\,cm}$ = 2270, ε = 97600), 471 nm, %III/II = 11, λ_{max}(diethyl ether) 420, 444, 464 nm; IR (KBr) cm^{-1}: 3435s (OH), 3038–2715s (CH), 2165w (C≡C), 1664s (conj. C=O), 1608s, 1568 m, 1520 m, 1406w, 1377w, 1356w, 1315w, 1267w, 1186 m, 1159w, 1044w, 1024w, 996w, 965s; MS [IP 70 eV, 200 °C: *m/z* (% rel. int.)] 430 (100, [$C_{30}H_{38}O_2$], measured: 430.287, calculated: 430.287), 428 (12, [*M*−2]), 412 (3, [*M*−18]), 397 (3), 299 (5), 261 (17), 247 (19), 235 (17), 221 (19), 207 (27), 195 (29), 165 (26), 157 (38), 143 (42), 131 (41), 119 (63), 105 (67), 91 (74), 69 (42), 55 (67), 43 (66), 41 (91); CD nm (Δε): 227 (−0.4), 240 (−0.8), 256 (−0.1), 277 (−0.4), 288 (0), 330 (+0.3), 334 (+0.2), 363 (+0.6); ^{1}H NMR ($CDCl_3$): δ 1.148 (s, 3 H, Me-16), 1.203 (s, 3 H, Me-17), 1.44 (m, 2 H, H-2_{ax} and OH), 1.84 (ddd, *J* ≈ 2 Hz, *J* 3.4 Hz, *J* 12.3 Hz, H-2_{eq}), 1.905 (s, 3 H, Me-19), 1.93 (d, 3 H, *J* ≈ 1 Hz, Me-18), 1.985 (s, 3 H, Me-20 or Me-20′), 2.010 (s, 3 H, Me-20 or Me-20′), 2.017 (d, 3 H, $J_{Me\text{-}19,H\text{-}10}$ ≈ 1 Hz, Me-19), 2.07 (ddd, 1 H, *J* ≈ 1 Hz, *J* 9.3 Hz, $J_{4,4}$ 17.1 Hz, H-4_{ax}), 2.44 (ddd, 1 H, *J* ≈ 1 Hz, *J* 4.1 Hz, $J_{4,4}$ 17.5 Hz, H-4_{eq}), 3.99 (m, 1 H, H-3), 6.29 (d, 1 H, $J_{14,15}$ 11.5 Hz, H-14), 6.36 (d, 1 H, $J_{11,12}$ 14.8 Hz, H-12), 6.45 (d, 1 H, $J_{14',15'}$ 11.4 Hz, H-14′), 6.47 (dq, 1 H, $J_{Me\text{-}19,H\text{-}10}$ 1.2 Hz, $J_{10,11}$ 11.6 Hz, H-10), 6.57 (dd, 1 H, $J_{10,11}$ 11.5 Hz, $J_{11,12}$ 14.7 Hz, H-11), 6.66 (dd, 1 H, $J_{14',15'}$ 11.5 Hz, $J_{15,15'}$ 14.1 Hz, H-15′), 6.67 (dd, 1 H, $J_{10',11'}$ 10.3 Hz, $J_{11',12'}$ 14.9 Hz, H-11′), 6.74 (d, 1 H, $J_{11',12'}$ 15.7 Hz, H-12′), 6.77 (dd, 1 H, $J_{14,15}$ 11.9 Hz, $J_{15,15'}$ 14.7 Hz, H-15), 6.95 (dq, 1 H, $J_{Me\text{-}19',H\text{-}10'}$ ≈ 1 Hz, $J_{10',11'}$ 10.4 Hz, H-10′), 9.455 (s, 1 H, H-8′).

*(all-*E*)-(3*R,8′*RS)-3,8′-Dihydroxy-7,8-didehydro-7′-apo-β-carotene* (**26**). Methyllithium (2.42 mmol, 1.73 ml of a 1.4 M solution in diethyl ether) was added dropwise to a stirred solution of the preceding C_{30}-hydroxy aldehyde **16** (0.23 g, 0.53 mmol) in dry diethyl ether (50 ml) at 20 °C under N_2 in the dark. The reaction mixture was stirred at 20 °C under an N_2 atm in the dark for 1 h and subsequently cooled to 0 °C. Water was added carefully to decompose the excess methyllithium and the product was extracted with diethyl ether. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and evaporated to dryness. CC of the resulting residue provided the two C-8′ epimeric C_{31}-diols **26**, inseparable by TLC (system 1) and HPLC (system 1), in a ca. 4:1 mixture (^{1}H NMR) as a red solid in 94% yield (0.22 g, 0.49 mmol), >99% pure [TLC (system 1), HPLC (system 1), ^{1}H NMR]. HPLC (system 2) indicated a mixture of the all-*E* isomers (67%) and three *Z* isomers (12+8+13%). A mixture of the pure all-*E* C-8′ epimeric diols **26** was obtained by recrystallisation of a aliquot from benzene. M.p. 138–141 °C

(evacuated tube); TLC (system 2) R_f=0.32; HPLC (system 1): t_R=19.8 min; UV–VIS: λ_{max}(hexane) 400, 421, 449 nm, %III/II=46, λ_{max}(diethyl ether) 400, 423, 450 nm, %III/II=42; IR (KBr) cm^{-1}: 3412s (OH), 3036–2881 m (CH), 2171w (C≡C), 1708w, 1629w, 1446w, 1363w, 1314w, 1262w, 1173w, 1074w, 1050 m, 963s; MS [IP 70 eV, 200 °C: *m/z* (% rel. int.)] 446 (45, [$C_{31}H_{42}O_2$], measured: 446.319, calculated: 446.319), 444 (14, [*M*−2]), 428 (61, [*M*−18]), 418 (10, [*M*−28]), 322 (13, [*M*−124]), 249 (13), 235 (13), 221 (17), 209 (17), 195 (21), 171 (21), 157 (31), 143 (3), 119 (43), 105 (50), 91 (74), 69 (28), 55 (51), 43 (100); ^{1}H NMR ($CDCl_3$): δ 1.144 (s, 3 H, Me-16), 1.120 (s, 3 H, Me-17), 1.29 and 1.31 (2d in a ca. 4:1 ratio, 3 H, $J_{Me\text{-}7',H\text{-}8'}$ 6.4 Hz, Me-7'), 1.45 (m, 1 H, H-2_{ax}), 1.82 (d, 3 H, $J_{Me\text{-}19',H\text{-}10'}$ 1.8 Hz, Me-19'), 1.84 (ddd, 1 H, $J\approx$2 Hz, *J* 3.6 Hz, $J_{2,2}$ 12.8 Hz, H-2_{eq}), 1.922 (s, 3 H, Me-18), 1.952 (s, 6 H, Me-20 and Me-20'), 2.002 (s, 3 H, Me-19), 2.08 (m, 1 H, H-4_{ax}), 2.43 (ddd, 1 H, $J\approx$1 Hz, *J* 7.4 Hz, $J_{4,4}$ 17.9 Hz, H-4_{eq}), 3.99 (m, 1 H, H-3), 3.99 and 4.29 (*q*, 1 H, $J_{Me\text{-}7',H\text{-}8'}$ 6.1 Hz, H-8'), 6.17 (d, 1 H, $J_{10',11'}$ 10.9 Hz, H-10'), 6.25 (m, 2 H, H-14 and H-14'), 6.33 and 6.35 (2d, 2 H, *J* 14.8 Hz and 15.1 Hz, H-12 and H-12'), 6.45 (dd, 1 H, $J_{Me\text{-}19,H\text{-}10}\approx$1 Hz, $J_{10,11}$ 11.5 Hz, H-10), 6.45–6.55 (m, 2 H, H-11 and H-11'), 6.63 (m, 2 H, H-15 and H-15').

*(all-*E*)-(3*R*)-Triophaxanthin* (**1**). (i) The preceding C_{31}-diol **26** (39.0 mg, 0.09 mmol) in dichloromethane (20 ml) was stirred with manganese dioxide (1.00 g) at 20 °C under N_2 in the dark for 12 h. The reaction mixture was filtered. UV–VIS spectroscopy indicated a complex mixture of products with main absorption bands at ca. 400 nm and 310 nm. An aliquot of the reaction mixture was subjected to preparative TLC (system 1). Three fractions were isolated. Fraction 1 (R_f=0.56) had λ_{max}(hexane) 442, 466, 500 nm, %III/II=124. The mass spectrum of fraction 1 showed only minor peaks higher than *m/z* 277 (60% of base peak *m/z* 43). Fraction 2 (R_f=0.44) had λ_{max}(hexane) 416, 435, 462 nm. Fraction 3 (R_f=0.35), which co-eluted with the substrate **26** by TLC (system 1), had λ_{max}(hexane) 400 nm. No yields were calculated.

(ii) The C_{31}-diol **26** (1.4 mg, 3.1 mmol) in dichloromethane (3 ml) was stirred with manganese dioxide (16.0 mg) at 20 °C under N_2 in the dark. The reaction was monitored by TLC (system 1) and UV–VIS spectroscopy. Almost complete conversion of the substrate **26** into three major products (fractions 1–3), was observed after 15 min. The reaction mixture was filtered and an aliquot was withdrawn for preparative TLC (system 2). The above-denoted fraction 2 was isolated and subjected to HPLC (system 1), which indicated a mixture of the all-*E* isomer (50% of total) and five *Z* isomers (3+3+6+11+27%) of the desired (3*R*)-triophaxanthin (**1**), as subsequently demonstrated by co-injection [HPLC (system 1)] with **1** prepared by manganese dioxide oxidation of **26** in acetone. No yields were calculated.

(iii) The C_{31}-diol **26** (65.0 mg, 0.15 mmol) in acetone (30 ml) was stirred with manganese dioxide (1.00 g) at 20 °C under N_2 in the dark. The reaction was monitored by TLC (system 2) and HPLC (system 1). Complete conversion of the substrate was observed after 1 h. Only traces of the by-products denoted as fraction 1 and fraction 3 above were observed by TLC. The reaction mixture was filtered and the solvent was evaporated off. CC of the resulting residue afforded **1** as a red solid in 57% yield (38.2 mg, 86.0 mmol), >99% pure [TLC (system 2), HPLC (system 1), ^{1}H NMR]. HPLC (system 1) indicated a mixture of the all-*E* isomer (67%) and three *Z* isomers (4+16+13%). The all-*E* isomer crystallised from benzene, ca. 93% pure [HPLC (system 1), ^{1}H NMR], containing ca. 7% benzene after 10 h at 20 °C under reduced pressure (0.01 mmHg). M.p. 182–183 °C (evacuated tube); TLC (system 2): R_f=0.45; HPLC (system 1): t_R=16.6 min; UV–VIS: λ_{max}(hexane) 420, 445, 473 nm, %III/II=23, λ_{max}(acetone) 418, 445 ($E^{1\%}_{1cm}$=1980, ε=87 900, corrected for 7% benzene in the crystalline sample: $E^{1\%}_{1cm}$=2130, ε=94 500), 469 nm, %III/II=13; IR (KBr) cm^{-1}: 3474s (OH), 3086–2864s (CH), 2168w (C≡C), 1640s (conj. C=O), 1606m, 1571m, 1524w, 1387w, 1364w, 1323w, 1231m, 1160w, 1057w, 1031w, 962s; MS [IP 70 eV, 200 °C: *m/z* (% rel. int.)] 444 (96, [$C_{31}H_{40}O_2$], measured: 444.302, calculated: 444.303), 442 (17, [*M*−2]), 428 (6, [*M*−16]), 426 (8, [*M*−18]), 279 (11), 223 (12), 222 (17, [*M*−222]), 209 (14), 197 (15), 195 (13), 183 (16), 161 (25), 145 (16), 143 (19), 119 (32), 105 (29), 97 (35), 91 (36), 85 (46), 71 (61), 69 (56), 57 (100), 43 (95); CD nm (Δε): 216 (0), 220 (−0.6), 230 (−0.2), 241 (−0.5), 255 (−0.1), 263 (−0.3), 270 (−0.2), 277 (−0.4), 286 (0), 305 (+0.1), 328 (+0.2), 338 (+0.1), 360 (+0.3); ^{1}H NMR ($CDCl_3$): δ 1.145 (s, 3 H, Me-16), 1.200 (s, 3 H, Me-17), 1.45 (m, 1 H, H-2_{ax}), 1.84 (ddd, 1 H, *J* 2.0 Hz, *J* 3.5 Hz, $J_{2,2}$ 12.3 Hz, H-2_{eq}), 1.92 (d, 3 H, $J\approx$1 Hz, Me-18), 1.94 (d, 3 H, $J_{Me\text{-}19',H\text{-}10'}$ Me-19'), 1.979 (s, 3 H, Me-20), 1.997 (s, 3 H, Me-20'), 2.05 (d, 3 H, $J_{Me\text{-}19,H\text{-}10}$ ≈1 Hz, Me-19), 2.06 (ddd, 1 H, *J* 1.1 Hz, *J* 8.4 Hz, $J_{4,4}$ 17.6 Hz, H-4_{ax}), 2.366 (s, 3 H, Me-7'), 2.43 (ddd, 1 H, $J\approx$1 Hz, *J* 6.0 Hz, $J_{4,4}$ 16.6 Hz, H-4_{eq}), 3.99 (m, 1 H, H-3), 6.28 (d, 1 H, $J_{14,15}$ 11.0 Hz, H-14), 6.36 (d, 1 H, $J_{11,12}$ 14.4 Hz, H-12), 6.40 (d, 1 H, $J_{14',15'}$ 11.0 Hz, H-14'), 6.46 (dq, 1 H, $J_{Me\text{-}19,H\text{-}10}$ 1.3 Hz, $J_{10,11}$ 11.4 Hz, H-10), 6.57 (dd, 1 H, $J_{10,11}$ 11.1 Hz, $J_{11,12}$ 14.1 Hz, H-11), 6.59 (dd, 1 H, $J_{10',11'}$ 11.8 Hz, $J_{11',12'}$ 14.1 Hz, H-11'), 6.67 (d, 1 H, $J_{11',12'}$ 15.0 Hz, H-12'), 6.69 (dd, 1 H, $J_{14',15'}$ 10.8 Hz, $J_{15,15'}$ 14.3 Hz, H-15'), 6.74 (dd, 1 H, $J_{14,15}$ 11.1 Hz, $J_{15,15'}$ 14.2 Hz, H-15), 7.14 (dq, 1 H, $J_{Me\text{-}19',H\text{-}10'}$ 1.5 Hz, $J_{10',11'}$ 11.1 Hz, H-10'); ^{13}C NMR ($CDCl_3$): δ 11.7 (C-19'), 12.8 and 12.9 (C-20 and C-20'), 18.1 (C-19), 22.5 (C-18), 25.6 (C-7'), 28.8 (C-16), 30.5 (C-17), 36.6 (C-1), 41.5 (C-4), 46.7 (C-2), 64.9 (C-3), 89.3 (C-7), 98.5 (C-8), 119.7 (C-9), 123.9 (C-11), 124.2 (C-6), 124.9 (C-11'), 129.8 (C-15'), 132.1 (C-15), 133.1 (C-14), 135.0 (C-10), 135.6 and 135.8 (C-13 and C-13'),

136.2 (C-14′), 137.6 (C-12), 137.7 (C-5), 137.8 (C-9′), 140.0 (C-10′), 144.5 (C-12′), 199.5 (C-8′).

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