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First Total Synthesis of (all-*E*)-(3*S*,5*R*,6*R*)-Paracentrone

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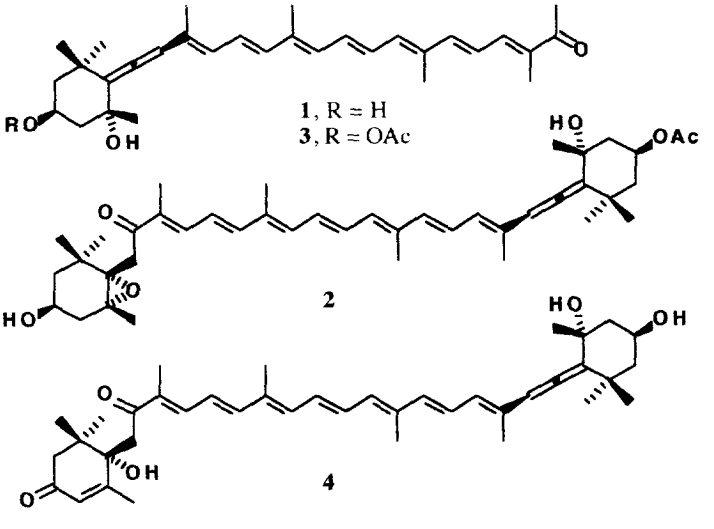
Abstract: (all-*E*)-(3*S*,5*R*,6*R*)-Paracentrone was synthesised in the optically active form in five steps in 52% overall yield from the available (2-*E*)-(4*R*)-((2*R*,4*S*)-2,4-dihydroxy-2,6,6-trimethylcyclohexylidene)-3-methyl-2,4-pentadien-1-ol, (all-*E*)-(7-formyl-2-methyl-2,4,6-octatrienyl)triphenylphosphonium bromide and (2-*E*)-(3-methyl-4-oxo-2-butenyl)-triphenylphosphonium bromide. Spectroscopic data for the title compound were in good accordance with data reported for the natural compound.

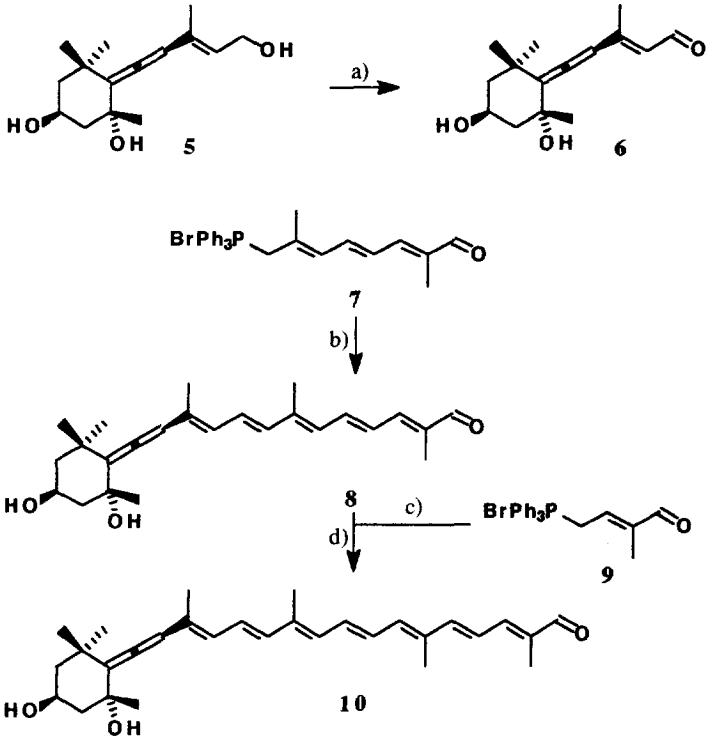
The structural elucidation of paracentrone (**1**), see Scheme 1, first isolated from the sea urchin *Paracentrotus lividus*, was reported by Weedon and co-workers in 1969.[2] Paracentrone (**1**) was the second naturally occurring C_{31}-methyl ketone carotenoid to be reported. Subsequently, Weedon and co-workers[3] reported the direct conversion, upon Oppenauer oxidation, of the allenic C_{40}-carotenoid fucoxanthin (**2**) into paracentrone 3-acetate (**3**). Hydrolysis of **3** afforded paracentrone (**1**) in 6% overall yield. It was inferred that paracentrone (**1**) probably results from degradation of dietary fucoxanthin (**2**) in the animal.[3] More recently, the formation of paracentrone upon basic hydrolysis of the marine C_{40}-carotenoid amarouciaxanthin A (**4**), isolated from the tunicate *Amaroucium pliciferum*, has been reported.[4]



Scheme 1.

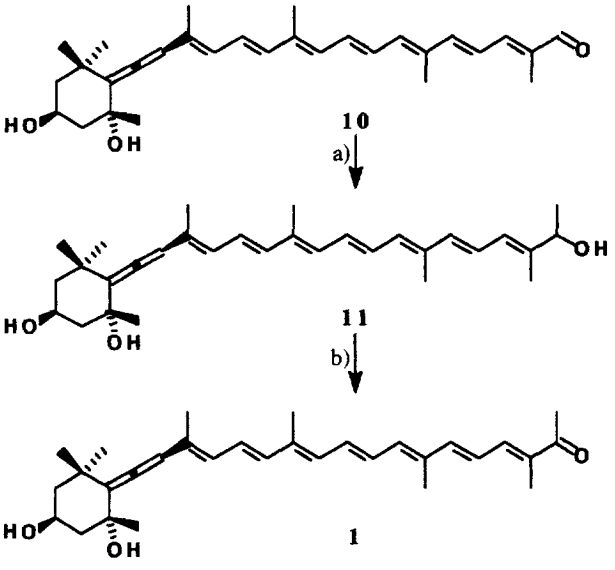
The first total syntheses of C_{31}-methyl ketone apocarotenoids, (all-*E*)-sintaxanthin and (all-*E*)-(3*R*)-3-hydroxysintaxanthin, were recently reported.[5] The $C_{15} + C_{10} + C_5 + C_1 = C_{31}$ strategy employed in the present synthesis of (all-*E*)-(3*S*,5*R*,6*R*)-paracentrone was adopted from a recent synthesis of two acetylenic C_{31}-methyl ketone apocarotenoids, (all-*E*)-(3*R*)-triophaxanthin[6] and (all-*E*)-(3*S*)-7'-apohopkinsiaxanthin.[7]

The C_{15}-allenic triol **5**, see Scheme 2, a well known intermediate employed in the synthesis of several allenic carotenoids[8] including mimulaxanthin,[9] neoxanthin,[10] peridinin[11] and fucoxanthin,[12] was recently prepared as a model compound for allenic carotenoids in an NMR study.[13,14] Allylic oxidation of **5** provided the C_{15}-allenic dihydroxy aldehyde **6**.[9,11] The aldehyde moiety of the C_{10}-phosphonium salt **7**, recently prepared for the synthesis of the sintaxanthins,[5] was protected as a dimethyl acetal, and a Wittig reaction with **6**, followed by hydrolysis of the acetal, provided the C_{25}-allenic dihydroxy aldehyde **8**. The aldehyde function of the C_5-phosphonium salt **9**,[15] recently employed in the synthesis of acetylenic C_{31}-methyl ketone apocarotenoids,[6,7] was protected as a dimethyl acetal, and a Wittig reaction with **8**, followed by hydrolysis of the acetal, provided the C_{30}-allenic dihydroxy aldehyde **10**, see Scheme 2.



Scheme 2. Reagents and conditions: a) MnO_2, THF, r.t. (92%); b) i) $HC(OCH_3)_3$, *p*-TsOH, MeOH, 30-35 °C, ii) NH_3, MeOH, 0 °C, iii) **6**, NaH, CH_2Cl_2, r.t., iv) AcOH - H_2O - CH_2Cl_2 1 : 1 : 5, 0 °C (94%); c) i) $HC(OCH_3)_3$, *p*-TsOH, MeOH, 30-35 °C, ii) NH_3, MeOH, 0 °C; d) i) NaH, CH_2Cl_2, r.t., ii) AcOH - H_2O - CH_2Cl_2 1 : 1 : 5, 0 °C (84%).

Treatment of the C_{30}-allenic dihydroxy aldehyde **10** with methyllithium provided the C-8' epimeric triols **11** with the desired C_{31}-skeleton, see Scheme 3. Finally, adjustment of the oxidation level by oxidation of the secondary allylic hydroxy group of **11**, afforded (all-*E*)-(3*S*,5*R*,6*R*)-paracentrone (**1**) as a deep red crystal powder. The overall yield of **1** over five steps from the C_{15}-allenic triol **5** was 52%. All physical data for synthetic (all-*E*)-(3*S*,5*R*,6*R*)-paracentrone (**1**)[16] were in good accordance with data previously reported for the natural compound.[2-4] A full account of the present work with complete experimental data will be published.[17]



Scheme 3. Reagents and conditions: a) MeLi, THF, r.t. (96%); b) MnO_2, acetone, r.t. (75%).

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16. M.p. 184-185 °C (evacuated tube); UV-VIS λ_{max} (hexane) 417, 439, 467 nm, %III/II = 54, λ_{max} (acetone) 416, 442 ($E^{1\%}_{1cm}$ = 1960, ε = 90600, corrected for 4% benzene in the crystalline sample: $E^{1\%}_{1cm}$ = 2050, ε = 95000), 464 nm, %III/II = 8, λ_{max} (diethyl ether) 417, 440, 464 nm, %III/II = 10; IR (KBr) cm^{-1} 3406s (OH), 3020-2863s (CH), 1926m (C=C=C), 1652s (C=O), 1606w, 1576w, 1528m, 1452m, 1365m, 1318w, 1278m, 1227m, 1155s, 1069w, 1040m, 958s; MS [IP 70 eV, 200 °C; *m/z* (% rel. int.)] 462 (34, [$C_{31}H_{42}O_3$], measured: 462.314, calculated: 462.313), 444 (28, [M-18]), 426 (24, [M-18-18]), 261 (7), 233 (11), 221 (10), 209 (13), 197 (20), 195 (12), 183 (13), 167 (29), 157 (34), 149 (27), 119 (32), 109 (29), 105 (32), 95 (15), 91 (32), 43 (100); CD nm (Δε) 222 (-0.9), 228 (-1.1), 240 (-0.8), 250 (-1.0), 261 (-0.8), 267 (-0.9), 350 (0), 366 (+0.3), 386 (0); ^{1}H NMR ($CDCl_3$) δ 1.067 (*s*, 3 H, Me-17), 1.35 (*m*, 1 H, H-2_{ax}), 1.334 (*s*, 3 H, Me-16), 1.349 (*s*, 3 H, Me-18), 1.41 (*m*, 1 H, H-4_{ax}), 1.809 (*s*, 3 H, Me-19), 1.94 (*d*, 3 H, $J_{Me\text{-}19',H\text{-}10'}$ 1.0 Hz, Me-19'), 1.96 (*m*, 1 H, H-2_{eq}), 1.985 (*s*, 3 H, Me-20), 1.991 (*s*, 3 H, Me-20'), 2.27 (*ddd*, 1 H, *J* 1.9 Hz, *J* 4.2 Hz, $J_{4,4}$ 13.3 Hz, H-4_{eq}), 2.364 (*s*, 3 H, Me-7'), 4.32 (*m*, 1 H, H-3), 6.034 (*s*, 1 H, H-8), 6.12 (*d*, 1 H, $J_{10,11}$ 11.3 Hz, H-10), 6.26 (*d*, 1 H, $J_{14,15}$ 11.1 Hz, H-14), 6.34 (*d*, 1 H, $J_{11,12}$ 15.1 Hz, H-12), 6.39 (*d*, 1 H, $J_{14',15'}$ 11.7 Hz, H-14'), 6.58 (*dd*, 1 H, $J_{10,11}$ 11.1 Hz, $J_{11,12}$ 15.1 Hz, H-11), 6.60 (*dd*, 1 H, $J_{10',11'}$ 11.8 Hz, $J_{11',12'}$ 15.8 Hz, H-11'), 6.62 (*dd*, 1 H, $J_{14',15'}$ 11.1 Hz, $J_{15,15'}$ 15.1 Hz, H-15'), 6.67 (*d*, 1 H, $J_{11',12'}$ 15.7 Hz, H-12'), 6.74 (*dd*, 1 H, $J_{14,15}$ 11.1 Hz, $J_{15,15'}$ 14.2 Hz, H-15), 6.94 (*dq*, 1 H, $J_{Me\text{-}19',H\text{-}10'}$ 1.0 Hz, $J_{10',11'}$ 10.2 Hz, H-10'); ^{13}C NMR ($CDCl_3$) δ 11.6 (C-19'), 12.8 and 12.9 (C-20 and C-20'), 14.0 (C-19), 25.6 (C-7'), 29.3 (C-16), 31.4 (C-18), 32.2 (C-17), 35.8 (C-1), 48.9 (C-4), 49.4 (C-2), 103.2 (C-8), 117.7 (C-6), 123.8 (C-11'), 125.6 (C-11), 128.3 (C-10), 129.4 (C-15'), 132.1 (C-14), 132.2 (C-15), 132.6 (C-9), 135.5 (C-14'), 136.2 (C-12), 137.1 (C-9'), 137.9 (C-13 and C-13'), 140.0 (C-10'), 144.5 (C-12'), 199.4 (C-8'), 202.4 (C-7).
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