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## TOTAL SYNTHESIS OF PROLYCOPENE

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Summary: A total synthesis of the tetra-Z-isomer (1, 'prolycopene') of lycopene found in fruits of the Tangerine tomato Lycopersicon esculentum, based on: (i) elaboration of the 22,6E-carbinol (4) from a Pd-coupling reaction between the vinyl bromide (2) and the Z-enynol(3)(ii) successive Wittig reactions between (6) and (7), [leading to (8)] and between (8) and (6), and (iii) partial catalytic hydrogenation of the bis-acetylene (9), is described.

Prolycopene is the trivial name given to the tetra-Z-isomer (1) of the carotenoid lycopene, which was first isolated by Zechmeister et al<sup>1</sup> from fruits of the Tangerine tomato Lycopersicon esculentum var. 'Tangella'. Together with its congeners 15Z-phytoene, 15Z,9'Z-phytofluene, 9Z,9'Z-5carotene and 92,7'2,9'2-neurosporene<sup>†</sup>, prolycopene is responsible for the characteristic tangerine colour of Tangella fruits compared to the normal red colour of the common commercial tomato. In previous work, using principally comparative p.m.r. and c.m.r. data with model poly-Z polyenes, we have established the tetra-Z-structure (1) for this intriguing naturally occurring isomer of lycopene<sup>2</sup>,  $\overline{3}$ . In this Letter we show how we have confirmed the stereochemical assignment given to prolycopene, by total synthesis of the pigment.

The symmetrical structure of prolycopene, accommodating two Z-disubstituted double bonds in addition to two Z-trisubstituted double bonds led us to design a synthesis of the molecule based on semi-hydrogenation of the bisacetylene (9), as a final step, which we planned to elaborate using the 2Z, 6E-phosphonium salt (6) and the  $C_{10}$ -trienedialdehyde (7) as key intermediates.

Thus, a Wittig condensation between 6-methyl-5-hepten-2-one and bromomethyltriphenylphosphonium bromide<sup>4</sup> (KOBu<sup>t</sup>,THF,-60°C to 25°C) first led to a 3:1 mixture of E-and Z-isomers of 1-bromo-2,6-dimethyl-1,5-heptadiene (81%), from which the E-isomer (2), b.p. 56°C at 0.6mmHg, $\delta_{\rm H}$ 5.9 (q,J1,:CH.Br),5.06 (br,:CH), 2.08-2.16(4H), 1.8(d,J1, :CMe), 1.68(Me), 1.6 (Me) was separated

by gas chromatography together with distillation<sup>5</sup>. A coupling reaction between (2) and Z-3-methyl-2-penten-4-yn-1-ol (3) in the presence of  $Pd(PPh_3)_{\Delta}-CuI-PrNH_2$  (25°C, 17h)<sup>6</sup> next led to the 2Z, 6E-isomer (4) of 3,7,11-trimethyldodeca-2,6,10-trien-4-yn-1-ol (70%), which was obtained as an oil, b.p. 150°C at 0.3mmHg,  $\delta_H 5.83(tq, J 6.5 and 1.4,:CH_2OH)$ , 5.43(:CH.C:), 5.08(br,Me<sub>2</sub>C.C<u>H</u>:) 4.35(d, J 6.5, CH<sub>2</sub>OH), 3.2(br, OH), 2.12-2.17(4H), 1.92(2 x :CMe), 1.69(:CMe), 1.61(:CMe); 6 152.8, 134.2(d), 132.4, 123.5(d), 121.7, 104.9(d), 93.1, 90.2, 61.7(t), 39.0(t), 26.5(t), 25.9(q), 23.6(q), 19.9(q), 17.9(q). The stereochemistry assigned to (4) followed conclusively from comparison of its n.m.r. spectral data with those of the corresponding 22,62-, 2E,62-, and 2E,6E-geometrical isomers which were synthesised independently via similar Pd-catalysed coupling reactions between pure Z-and E-isomers of the bromide (2) and pure Z- and E- isomers of the pentenynol (3)<sup>7</sup>. Bromination of the  $2\underline{Z}$ ,  $6\underline{E}$ -trienynol (4), using 1, 2dibromotetrachloroethane-triphenylphosphine,<sup>8</sup> then led to the bromide (5)(98%) which was immediately reacted with triphenylphosphine producing the key 2Z,6E-phosphonium salt intermediate (6) (85%),  $\delta_{\rm H}$  7.7-7.9 (m, 15H), 5.65 (br,:CH CH<sub>2</sub>), 5.21 (:CH.C:), 5.04 (br,Me<sub>2</sub>C.CH:), 4.94 (dd, J6 and 12, CH2PPh3), 2.07-2.12 (m,4H), 1.83(d, J6:CMe), 1.72(:CMe), 1.69(:CMe), 1.60 (:CMe)<sup>9</sup>.

Condensation between the phosphonium salt (6) and the trienedialdehyde  $(7)^{10}$  (2M ag.NaOH.ClChoCHoCl 25°C 2b) followed (7) (2M aq.NaOH,ClCH<sub>2</sub>CH<sub>2</sub>Cl, 25°C, 2h) followed by chromatography produced the C<sub>25</sub>-9<u>Z</u>hepta-enynal (8) (36%) as a clear orange oil, $\lambda_{max}$  (hexane) 391(26,800), 411(32,000), 434(24,300)nm.,  $\delta_{H}$ 9.45 (CHO), 6.29-6.72(m,7H), 5.53(:CH), 5.1 (br,:CH), 2.17(4H), 2.02(Me), 2.0(Me), 1.99(Me), 1.88(Me), 1.70(Me), 1.62(Me);  $\delta_{C}$  39.0(t), 26.6(t), 25.7(q), 23.8(q), 19.7(q), 17.8(q), 13.1(q), 9.7(q). The stereochemistries assigned to the carbon-to-carbon double bonds in (8) followed from inspection of shift data for the vinyl methyl resonances in the c.m.r. spectrum, and comparison of these data with those of model compounds described in our earlier work<sup>2,11</sup>. Significantly the c.m.r. absorptions at 623.8 (C-9-Me) and 6 13.1 (C-13-Me) define the 9Z,11E,13E stereochemistry of the newly incorporated C-9 to C-14 triene portion of (8). A second Wittig condensation between the Z-phosphonium salt (6) and (8) (2M aq.NaOH,ClCH<sub>2</sub>CH<sub>2</sub>Cl, 25°C, 1.75h.), then produced the <u>bis</u>-acetylene (9) as a 2:1 mixture of  $9\underline{Z}$ ,  $9'\underline{Z}$ - and  $9\underline{Z}$ ,  $9'\underline{Z}$ ,  $11'\underline{Z}$ -geometrical isomers in a combined yield of 61%. The mixture of isomers was treated briefly and cautiously with a very dilute solution of iodine in benzene (monitoring by h.p.l.c.) and afterwards thoroughly washed with thiosulphate solution. Chromatography and crystallisation then led to the symmetrical 92,92'-bisacetylene (9) as orange crystals, m.p. 110°C (ethanol-hexane), $\lambda_{max}$ 419(37,000), 443(55,600), 472(49,100)nm., $\delta_{\rm H}$  6.8(dd,<u>J</u> 15 and 11, 2H) 6.6(AA' of AA'BB' spin system, C15, C15'-H), 6.35(d, J15, 2H), 6.29(d, J11, 2H), 6.29(d, J 11, 2H), 6.25(BB' of AA'BB' spin system, C14, C14'H), 5.52(2x:CH),







(2)











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5.1(br,2H), 2.16(8H), 1.98(4 x:CMe), 1.95(2 x :CMe), 1.69(2 x :CMe), 1.62(2 x :CMe);  $\delta_{\rm C}$ 152.1,137.3, 136.6, 135.7, 133.1, 132.3, 130.2, 127.2, 123.5, 119.9, 105.4, 94.9, 92.4, 39.0, 26.4, 25.8, 23.6, 29.6, 17.8, 12.8 p.p.m. Partial catalytic hydrogenation of the <u>bis</u>-acetylene (9) in ethyl acetate in the presence of Lindlar's catalyst, although somewhat precarious,<sup>12</sup> finally led to the tetra-<u>Z</u>-polyene (1)( $\sim$ 15%) which showed identical chromatographic behaviour and spectoscopic data to those of naturally derived prolycopene<sup>13</sup>.

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- 13. In contemporaneous studies U. Hengartner, K. Bernhard, G. Englert and E. Glinz have also achieved a synthesis of 72,92,7'2,9'2-lycopene; Paper presented at 8th International Symposium on Carotenoids, Boston, Massachusetts, July 1987.

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