Synthesis C. Wu et al. Paper

Practical Synthesis of ε-Carotene

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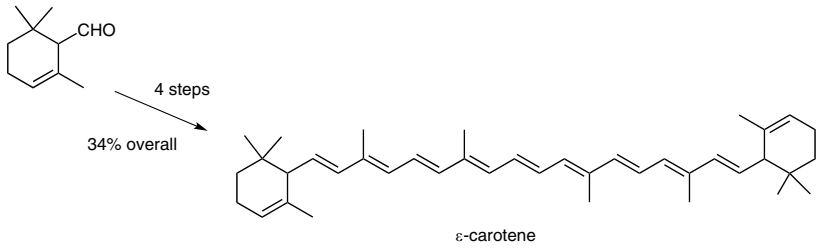


Received: 17.07.2014
Accepted after revision: 07.11.2014
Published online: 05.12.2014
DOI: 10.1055/s-0034-1378941; Art ID: ss-2014-h0452-op

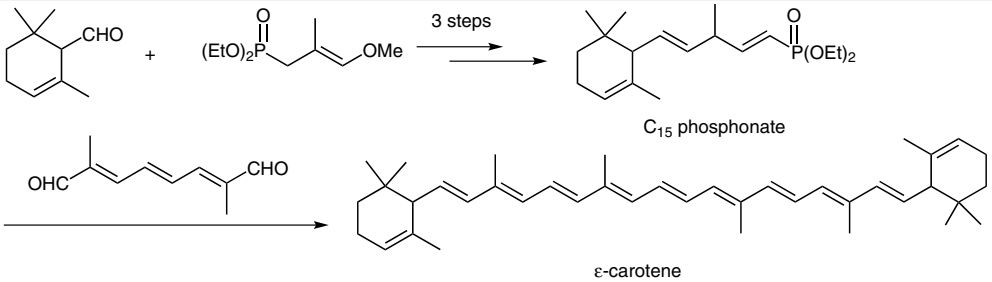
Abstract A novel route for the total synthesis of ε-carotene is described. The synthesis is based on a condensation between α-cyclocitral and diethyl [(2*E*)-3-methoxy-2-methylprop-2-en-1-yl]phosphonate to give a C_{14} enol ether, hydrolysis of the C_{14}-enol ether to a give a C_{14} aldehyde, and a modified Wittig–Horner reaction of the C_{15} phosphonate from the C_{14} aldehyde and a C_{10} triene dialdehyde to give ε-carotene. The synthetic steps are easily performed and are practical for large-scale production.

Key words total synthesis, Wittig reactions, carotenes, isomerizations

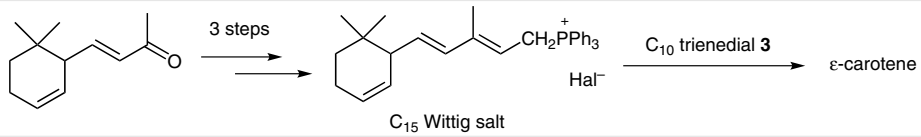
Carotenoids are a large group (more than 750 different members have been described) of lipid-soluble pigments that are biosynthesized in photosynthetic plants, bacteria, some fungi, and algae.[1] In these organisms, carotenoids are involved in photosynthesis and in photoprotection.[2] The biological functions of some of these highly conjugated polyenes have been elucidated, and organic syntheses have been designed to produce these invaluable natural products in large quantities for use as medications and nutraceuticals for improving human health. Most carotenoids have a highly efficient free-radical scavenging activities that can be beneficial in the prevention of some of cancers and cardiovascular disease.[3] ε-Carotene is a member of the carotenoid family that is present in carrots and tomatoes, alongside β-carotene and lycopene. Because ε-carotene has an α-end group, it would be expected to possess similar functional roles to β-carotene and lycopene in living systems. For this reason, we wish to report a practical method for the total synthesis of ε-carotene (Scheme 1).

The synthesis of carotenoids has evolved in parallel to the development of synthetic methods for the construction of polyenes.[4] The Wittig reaction has been used as the main shortcut for this purpose. The most classical route to ε-carotene was devised by Weedon and co-workers in 1965;[4a] this involved the stepwise $C_{15} + C_{10} + C_{15}$ double Wittig reaction shown in Scheme 2. An excess of the C_{15} Wittig salt was treated with (2*E*,4*E*,6*E*)-2,7-dimethylocta-2,4,6-trienedial (**3**) to yield ε-carotene. The C_{15} Wittig salt was prepared from α-ionone in three steps in an overall yield of 45%.

We recently reported syntheses of β-carotene, vitamin A, and lycopene by a stepwise $C_{15} + C_{10} + C_{15}$ Wittig–Horner condensation[5] in which C_{15} phosphonate building blocks, instead of C_{15} triphenylphosphonium salts, were designed and coupled with trienedial **3**. Because the use of phospho-



Scheme 1 Synthesis of ε-carotene



Scheme 2 Weedon's method for the synthesis of ε-carotene

nate should avoid some of the difficulties associated with the use of phosphonium salts (for example, the separation of triphenylphosphine oxide from the products), our strategy for synthesizing ε-carotene involved using the corresponding phosphonate to couple with trienedial **3**. The entire synthesis is shown in Scheme 3. In this route, the key intermediate C_{15} phosphonate can be prepared from α-cyclocitral and diethyl [(2*E*)-3-methoxy-2-methylprop-2-en-1-yl]phosphonate (**5**) in three steps. The starting material **5** can be synthesized according to the literature.[6] α-Cyclocitral (**4**), tetraethyl methylenebisphosphonate (**8**) and trienedial **3** of technical grade were purchased.

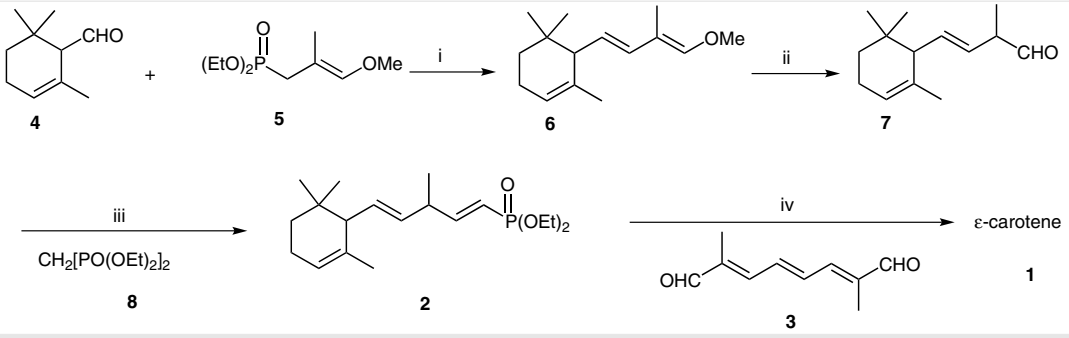
The condensation of α-cyclocitral (**4**) with phosphonate **5** in the presence of potassium *tert*-butoxide at –20 °C gave the C_{14} enol ether **6** in 70% yield. The product was a colorless liquid that could be purified by distillation. In this step, the key substrate **5** was initially converted into its corresponding carbanion by the base. This carbanion was stabilized by the presence of the double bond and the phosphonate group, permitting the condensation to occur smoothly. We have previously used phosphonate **5**, with its interesting structure, in our synthesis of another carotenoid, lycopene.[7]

The C_{14} enol ether **6** was then readily converted into the corresponding C_{14} aldehyde **7** in 72% yield. The hydrolysis proceeded under mild conditions with 4-toluenesulfonic acid as the catalyst, so that the original double bond system remained in balance and the nonconjugated C_{14} aldehyde **7** was obtained.

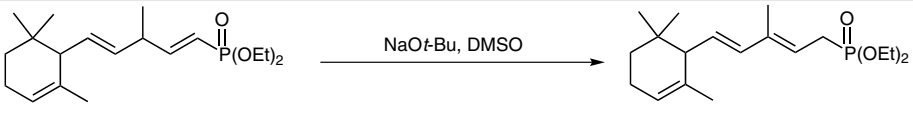
Next, the vinyl C_{15} phosphonate **2v** was obtained in 90% yield by condensation of the C_{14} aldehyde **7** with tetraethyl methylenebisphosphonate (**8**) in the presence of sodium hydride at 10–15 °C; again, the product could be purified by distillation.

All that now remained to complete our synthesis of ε-carotene (**1**) was to carry out a second Wittig–Horner reaction of the C_{15} phosphonate **2v** and the C_{10} triene aldehyde **3** in the presence of sodium *tert*-butoxide. However, to obtain the structure of ε-carotene (**1**), the vinyl C_{15} phosphonate **2v** needed to be converted into the corresponding allyl C_{15} phosphonate **2a** before condensation with the C_{10} trienedial **3** (Scheme 4). Babler and Schlidt[8] reported that an analogous vinyl phosphonate readily isomerized to give the corresponding allyl phosphonate in the presence of a base catalyst, so we surmised that this process might also proceed smoothly with vinyl C_{15} phosphonate **2v**. To confirm this conjecture, a mixture of vinyl C_{15} phosphonate **2v** and sodium *tert*-butoxide in dimethyl sulfoxide was stirred at –15 °C for three hours and then the mixture was hydrolyzed. We were amazed to find that isomerization of vinyl C_{15} phosphonate **2v** into allyl C_{15} phosphonate **2a** occurred smoothly, as shown by ^{1}H NMR and ^{13}C NMR spectroscopy. ε-Carotene **1** was subsequently obtained in 75% yield by adding trienedial **3** to the isomerized mixture at –15 °C.

In summary, a new route has been developed for the total synthesis of ε-carotene (**1**) with a total yield of 34%, in which a Wittig–Horner condensation is used as the sole method for chain extension. The synthesis starts from α-cyclocitral (**4**); neither the intermediate C_{14} enol ether **6** nor the C_{15} phosphonates **2** have been reported before. Because all the synthetic steps are readily performed and all the key



Scheme 3 *Reagents and conditions*: (i) KO*t*-Bu, THF–DMSO, –20 °C, 70%; (ii) PTSA, acetone–H_2O, 20–25 °C, 72%; (iii) NaH, toluene, 10–15 °C, 90%; (iv) NaO*t*-Bu, THF–DMSO, –20 to 10 °C, 75%.



vinyl C_{15} phosphonate **2v** allyl C_{15} phosphonate **2a**

Scheme 4 The isomerization of vinyl C_{15} phosphonate **2** to allylic C_{15} phosphonate **2**

building blocks can be prepared on a large scale, the synthetic route discussed here might be useful as a practical route for the synthesis of ε-carotene.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE DMX II I400M spectrometer. Samples were dissolved in $CDCl_3$, which provided the deuterium lock for the spectrometers. TMS or residual $CHCl_3$ was used as an internal standard. GC-MS measurements were performed on an Agilent MS 5973N-GC6890N. HRMS measurements were performed on a Waters Micromass GCT Premier. GC analysis was carried out on a Shanghai Tianmei 7890F instrument.

6-[(1*E*,3*E*)-4-Methoxy-3-methylbuta-1,3-dien-1-yl]-1,5,5-trimethylcyclohexene (6)

Phosphonate **5** (24.4 g, 0.11 mol) was added dropwise over 30 min to a solution of KO*t*-Bu (12.3 g, 0.11 mol) in 8:1 anhyd THF–DMSO (50 mL) at –20 °C min under N_2. The mixture was stirred at –20 °C for 1 h and then a solution of α-cyclocitral (**4**; 15.2 g, 0.1 mol) in 8:1 THF–DMSO (10 mL) was added dropwise over 30 min. The mixture was stirred for another 30 min until the reaction was complete (GC). H_2O (50 mL) and Et_2O (100 mL) were added, and the mixture was stirred for another 10 min. The organic layer was separated, washed with 5% aq NaCl (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude product (GC content 98.6%) as a colorless liquid; yield: 15.4 g (70%); bp 93–95 °C (1 mmHg).

IR (film): 3120, 1683, 1657, 1250 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 3 H, CH_3), 0.81 (s, 3 H, CH_3), 1.15–1.21, 1.42–1.49 (m, 2 H, CCH_2CH_2), 1.59 (s, 3 H, $CHCCH_3$), 1.62 (s, 3 H, $OCHCCH_3$), 2.00–2.02 (m, 2 H, CH_2CH), 2.18 (d, *J* = 9.6 Hz, 1 H, $CCHCH$), 3.61 (s, 3 H, OCH_3), 5.38 (dd, *J* = 9.6, 15.6 Hz, 1 H, $CHCH$=CH), 5.38–5.39 (m, 1 H, CH_2CH), 5.81 (s, 1 H, C=CHO), 6.50 (d, *J* = 15.6 Hz, 1 H, CH=CHC).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 23.1, 23.0, 27.1, 27.6, 31.9, 32.2, 55.1, 59.6, 112.0, 120.4, 126.1, 129.1, 134.9, 143.8.

^{13}C DEPT135 (100 MHz, $CDCl_3$): δ = 14.7, 23.0 (–), 23.1, 27.1, 27.6, 31.9 (–), 55.1, 59.6, 120.4, 126.1, 129.1, 143.8.

GC-MS: *m*/*z* (%) = 220, 177 (100), 121, 109, 93, 77, 69, 65, 55, 43.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{24}O$: 220.1827; found: 220.1824.

(3*E*)-2-Methyl-4-(2,6,6-trimethylcyclohex-2-en-1-yl)but-3-enal (7)[9]

A three-necked flask was charged with enol ether **6** (11.0 g, 0.05 mol), THF (100 mL), PTSA (1.5 g), and H_2O (22 g) under N_2, and the mixture was stirred at 20–25 °C for 24 h. When hydrolysis was complete (GC), 9% aq $NaHCO_3$ (20 mL) was added and the THF was removed under reduced pressure. Cyclohexane (100 mL) was added and the organic layer was washed with H_2O (30 mL), dried, and concentrated in vacuo to give a crude product (GC content 73.1%); yield: 10.1 g (72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (s, 3 H, CH_3), 0.89 (s, 3 H, CH_3), 1.20 (d, *J* = 3.4 Hz, 3 H, $CHCH_3$), 1.38–1.45 (m, 2 H, CH_2CH_2C), 1.58 (s, 3 H, CCH_3), 2.0 (m, 2 H, CH_2CH_2C), 2.13 (d, *J* = 4.4 Hz, 1 H, CCHC), 3.06–3.11 (m, 1 H, CHCHO), 5.32–5.34 (m, 1 H, CH_2CHC), 5.36–5.47 (m, 2 H, CH=CH), 9.56 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 22.7, 23.0 (–), 26.8, 27.5, 31.5 (–), 50.0, 54.5, 121.2, 127.3, 135.5, 201.7.

^{13}C DEPT135 (100 MHz, $CDCl_3$): δ = 14.7, 23.0 (D), 23.1, 27.1, 27.6, 31.9 (D), 55.1, 59.6, 120.4, 126.1, 129.1, 143.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{22}O$: 206.1671; found: 206.1669.

Diethyl [(1*E*,4*E*)-3-Methyl-5-(2,6,6-trimethylcyclohex-2-en-1-yl)penta-1,4-dien-1-yl]phosphonate (2v)

A solution of tetraethyl methylenebisphosphonate (**8**; 31.5 g, 0.11 mol) in toluene (80 mL) was added dropwise over 30 min to a solution of NaH (60% content, 4 g, 0.1 mol) in toluene (20 mL) at 10–15 °C under N_2, and the mixture was stirred for 30 min. A solution of aldehyde **7** (18.5 g, 0.09 mol) in toluene (30 mL) was added dropwise over 30 min at 10–15 °C, and the mixture was stirred for a further 30 min. H_2O (80 mL) was added and the mixture was stirred for 10 min. The organic layer was washed with 10% aq NaCl (80 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude product (GC content 94.3%) as a pale-brown liquid; yield: 32.3 g (90%). This was purified by distillation in vacuo (~130 °C, 1 mmHg).

IR (film): 1626, 1596, 1247, 1026, 961 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (s, 3 H, CH_3), 0.88 (s, 3 H, CH_3), 1.15 (d, *J* = 6.8 Hz, 3 H, $CHCHCH_3$), 1.33 (t, *J* = 6.8 Hz, 6 H, 2 × OCH_2CH_3), 1.56 (s, 3 H, $CHCCH_3$), 1.41–1.43, 1.73–1.74 (m, 2 H, 2 × $CHCH_2CH_2$), 1.99–2.04 (m, 2 H, $CHCH_2CH_2$), 2.07 (d, *J* = 8.8 Hz, 1 H, $CCHCH$), 2.99–3.03 (m, 1 H, $CHCH_3$), 4.03–4.10 (m, 4 H, 2 × OCH_2), 5.29–5.30, 5.31–5.32 (m, 2 H, $CHCH$=$CHCH$), 5.38–5.39 (m, 1 H, CH_2CH), 5.62 (m, 1 H, CH=CHP), 6.70–6.77 (m, 1 H, CH=CHP).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 16.4, 19.4, 22.8, 23.1, 27.0, 27.5, 31.6, 31.9, 41.0, 54.4, 61.6, 61.7, 115.1 (d, *J* = 187.3 Hz, CP), 120.9, 132.0, 133.0, 134.1, 157.3.

^{13}C DEPT135 (100 MHz, $CDCl_3$): δ = 16.3, 16.4, 19.4, 22.8, 23.1 (–), 27.0, 27.5, 31.6 (–), 41.0, 54.4, 61.6 (–), 61.7 (–), 115.1 (d, *J* = 187.3 Hz, CP), 120.9, 132.0, 133.0, 157.3.

GC-MS: *m*/*z* (%) = 340, 325, 284, 219, 146 (100), 131, 119, 105, 91, 81, 55, 41.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{33}O_3P$: 340.2167; found: 340.2163.

Diethyl [(2*E*,4*E*)-3-Methyl-5-(2,6,6-trimethylcyclohex-2-en-1-yl)penta-2,4-dien-1-yl]phosphonate (2a)[10]

A sample was taken during the next step, the synthesis of ε-carotene (**1**), to show that the vinyl C_{15} phosphonate **2v** rearranged completely into the allyl C_{15} phosphonate **2a**.

IR (film): 1615, 1587, 1252, 1026, 964 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3), 1.15–1.19, 1.40–1.47 (m, 2 H, CCH_2CH_2), 1.31 (t, *J* = 7.0 Hz, 6 H, 2 × CH_2CH_3), 1.57 (s, 3 H, CH_3), 1.77 (d, *J* = 4.0 Hz, 3 H, CH_3), 1.98–2.01 (m, 2 H, CCH_2CH_2), 2.14 [d, *J* = 9.6 Hz, 1 H, CCHCH(C)], 2.70 (dd, *J* = 8.0, 22.8 Hz, 2 H, $CHCH_2P$), 4.05–4.15 (m, 4 H, 2 × OCH_2CH_3), 5.40–5.47 (m, 3 H, 3 × =CH), 6.06 (d, *J* = 15.2 Hz, 1 H, CH=CHC).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 16.4, 16.5, 23.0, 23.1, 26.8 (d, *J* = 139.4 Hz, CH_2P), 27.0, 27.6, 31.7, 32.3, 54.6, 61.9, 62.0, 117.5, 120.8, 130.1, 134.4, 135.2, 137.8.

^{13}C DEPT135 (100 MHz, $CDCl_3$): δ = 12.8, 16.4, 16.5, 23.0, 23.1 (–), 26.8 (–; d, *J* = 139.4 Hz, CH_2P), 27.0, 27.6, 31.7 (–), 54.6, 61.9 (–), 62.0 (–), 117.5, 120.8, 130.1, 135.2.

GC-MS: *m*/*z* (%) = 340, 218 (100), 189, 161, 138, 123, 91, 81, 55, 41.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{33}O_3P$: 340.2167; found: 340.2169.

ε-Carotene (1)[4a]

A solution of NaO*t*-Bu (24 g, 0.25 mol) in DMSO (50 mL) was added dropwise over 30 min to a solution of vinyl C_{15} phosphonate **2v** (94 g, 0.275 mol) in toluene (250 mL) at –15 °C under N_2. The mixture was stirred for a further 3 h to ensure that the vinyl phosphonate **2v** was converted into the carbanion of the corresponding allyl C_{15} phosphonate **2a**. A solution of dial **3** (20.5 g, 0.125 mol) in THF (50 mL) was added dropwise over 20 min, and the mixture was stirred for another 12 h at 10 °C. When the reaction was complete, H_2O (500 mL) was added. A first fraction of a crude red solid product precipitated and was collected by filtration. The filtrate was separated and the inorganic layer was extracted with toluene (2 × 100 mL). The organic layers were combined, washed with H_2O (2 × 100 mL) and sat. aq NaCl (3 × 75 mL), dried ($MgSO_4$), and evaporated in vacuo to obtain a residue. The residue was treated with EtOH (100 mL) to precipitate a second fraction of the crude product. The first and second fractions of the crude product were combined and recrystallized from EtOH–CH_2Cl_2 (1:5) to give the pure product (HPLC content 96.8%); yield: 51.2 g (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (s, 6 H, 2 × CH_3), 0.90 (s, 6 H, 2 × CH_3), 1.15–1.21, 1.42–1.49 (m, 4 H, 2 × CH_2), 1.59 (s, 6 H, 2 × CH_3), 1.91 (s, 6 H, 2 × CH_3), 1.96 (s, 6 H, 2 × CH_3), 2.01–2.05 (m, 4 H, 2 × CH_2), 2.18 (dd, *J* = 1.2, 4.0 Hz, 2 H, 2 × CH), 5.41 (s, 2 H, 2 × =CH), 5.50–5.56 (m, 2 H, 2 × =CH), 6.09–6.11 (m, 2 H, 2 × =CH), 6.13–6.16 (m, 2 H, 2 × =CH), 6.23–6.27 (m, 2 H, 2 × =CH), 6.32–6.36 (m, 2 H, 2 × =CH), 6.58–6.64 (m, 4 H, 4 × =CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 13.2, 23.1, 23.2, 27.1, 27.7, 31.7, 32.6, 54.9, 120.8, 125.0, 130.0, 130.3, 131.0, 132.4, 134.5, 135.6, 136.2, 136.4, 137.2.

^{13}C DEPT135 (100 MHz, $CDCl_3$): δ = 12.8, 13.2, 23.1, 23.2 (–), 27.1, 27.7, 31.7 (–), 54.9, 120.8, 125.0, 130.0, 130.3, 131.0, 132.4, 136.2, 137.2.

Acknowledgment

We acknowledge the National Natural Science Foundation of China (No. 21176156 and No. 81202411) and Research Fund of Zhejiang Educational Committee of China (Y 201431839).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378941.

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