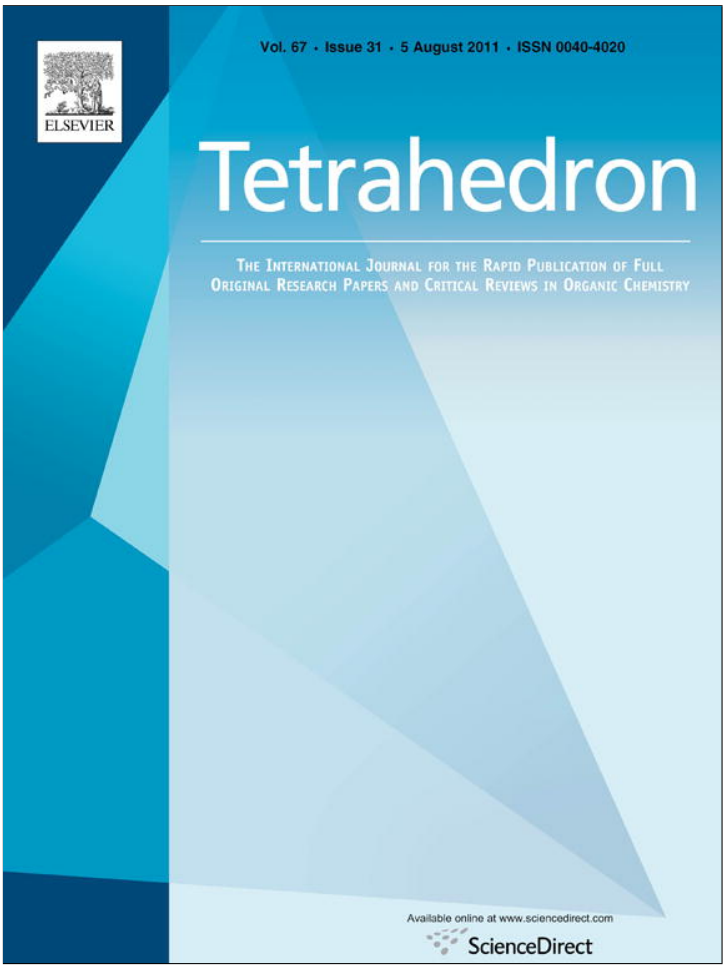

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A novel and practical synthetic route for the total synthesis of lycopene

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ABSTRACT

A novel route for the total synthesis of lycopene **1** is described. The synthesis is based on: (i) a condensation between 4,4-dimethoxy-3-methylbutanal **4** and methylenebisphosphonic acid tetraethyl ester **5**, leading to the C6-phosphonate **6**, followed by (ii) a modified Wittig–Horner reaction between **6** and 6-methyl-5-hepten-2-one **7** producing dimethoxy-3,5,9-triene **8**, and (iii) another modified Wittig–Horner reaction between C15-phosphonate **2** and C10-triene dialdehyde **3** producing all-*E*-lycopene. The synthetic steps are easily operated and practical for the large-scale production.

1. Introduction

Lycopene **1**, a member of carotenoids, is a red pigment substance found in tomatoes with 13 double bonds. It exhibits higher radical scavenging ability[1] compared to β-carotene and gives the health protection against a variety of serious disorders including cancer, heart disease, and degenerative eye diseases.[2,3] Accordingly it has been widely used as an excellent additive in food, fodder and drugs.[4] These interesting biological activities as well as its unique molecular architecture have stimulated a number of synthetic efforts to produce lycopene[5] since the first synthesis in 1950,[6] in which the most concern is how to introduce newly conjugated carbon-carbon double bonds. The Wittig reaction has been used as a main shortcut for this purpose, and the most representative disconnection of lycopene **1** based on the available C15 Wittig salts and the C10-triene dialdehyde **3** building blocks are shown in Scheme 1.[7–10] But the use of costly and toxic reagent triphenyl-phosphine will lead to the difficult post-handling and environmental pollution because of the formation of by-product triphenyl-phosphine oxide. Wittig–Horner reaction, as an improved method, in which C15 Wittig–Horner phosphonate was used as the synthon, can resolve the above problems (Scheme 1). Babler et al.[9] described a four-step route for the conversion of pseudoionone to lycopene, in which allenic phosphonate reagent and allylicphosphonate were employed as two key intermediates instead of triphenyl-phosphine halide salts. But the reaction conditions for the synthesis of allenic phosphonate from 3° propargylic alcohol and dialkyl chlorophosphite was too rigorously, and subsequent partial hydrogenation of allenic phosphonate was somewhat too difficult to finish with high selectivity.

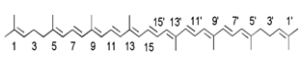
In this paper, we report a practical approach for the synthesis of lycopene[†] by reacting C15-phophonate **2** and the known C10-triene dialdehyde **3**, and the key intermediate C15-phophonate **2** could be synthesized in four steps by using 4,4-dimethoxy-3-methylbutanal **4** as starting material (Scheme 2). Here Wittig–Horner reaction is adopted as an efficient approach to introduce new double bonds under mild reaction conditions. The starting material 4,4-dimethoxy-3-methylbutanal **4** was obtained according to the literature,[11] and 6-methyl-5-hepten-2-one **7** and C10-triene dialdehyde **3** of technical grade were purchased.

2. Results and discussion

The condensation between 4,4-dimethoxy-3-methylbutanal **4** and methylenebisphosphonic acid tetraethyl ester **5**, in the presence of NaH at 10–15 °C gave propenyl-C6-phosphonate **6** with a yield of 86.9%. The product **6** was a colorless liquid, and can be purified by distillation.

Next, dimethoxy-3,5,9-triene **8** was obtained from condensation of propenyl-C6-phosphonate **6** with 6-methyl-5-hepten-2-one

[†] The system of numbering carotenoids recommended by I.U.P.A.C. is used throughout this paper, i.e., lycopene.



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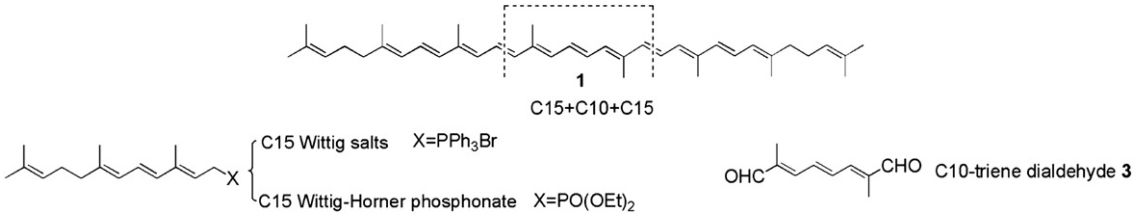
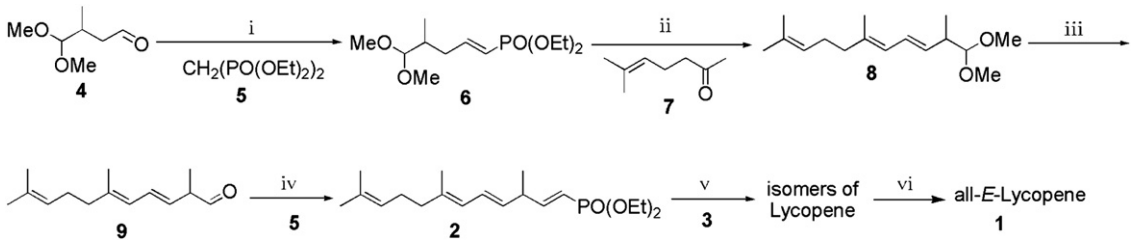
7 directly. According to our previous study on synthesis of Vitamin A,[12] an analogous rearrangement of the double bond on propenyl-C6-phosphonate **6** occurred with a mechanism proposed as Scheme 3.

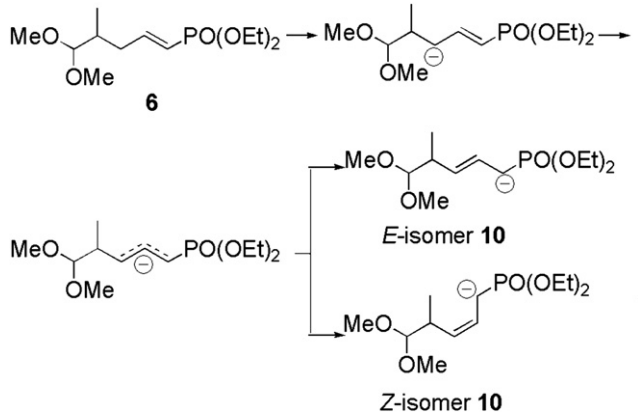
Dimethoxy-3,5,9-triene **8** can be easily converted to the corresponding C14-aldehyde **9** in the presence of *p*-TSA in 86.8% yield. The product C14-aldehyde **9** was still composed of four isomers as well as the stereochemistry of dimethoxy-3,5,9-triene **8**.



Scheme 1. C15+C10+C15 disconnection of Lycopene **1** via Wittig reaction or Wittig–Horner reaction.



Scheme 2. Reagents and conditions: (i) NaH, toluene, 10–15 °C, 86.9%; (ii) KO*t*-Bu, THF, and DMSO, −30 to −25 °C, 65.3%; (iii) THF, *p*-TSA, 20–25 °C, 86.8%; (iv) NaH, toluene, 10–15 °C, 88.8%; (v) KO*t*-Bu, THF and DMSO, −30 to −25 °C, 61.6%; (vi) ethanol, 75–80 °C.



Scheme 3. The proposed mechanism of the rearrangement from propenyl-C6-phosphonate **6** to allylic-C6-phosphonate **10**.

Thereby the condensation started from the rearrangement of propenyl-C6-phosphonate **6** at −30 to −25 °C in the presence of KO*t*-Bu, and the corresponding carbanion of allylicphosphonate **10** was obtained in about 1 h with the color of reaction mixture turning deep red from light yellow. At the same time, a mixture of *Z*- and *E*-allylicphosphonate **10** was observed when sampling a few microliters of the reaction mixture and analyzed by GC–MS. The mixture of the two isomers was used without separation in the next step.

Then a Wittig–Horner reaction between allylic-C6-phosphonate **10** and 6-methyl-5-hepten-2-one **7** gave colorless liquid dimethoxy-3,5,9-triene **8**, which was composed of 3*E*,5*Z*-; 3*Z*,5*Z*-; 3*E*,5*E*-; 3*Z*,5*E*- (major product) four isomers with the ratio of about 1:2:2:4. The stereochemistry was assigned to **8** according to the analysis of its ^{13}C NMR spectroscopic data presented in Fig. 1. No separation for the four isomers was needed before using in the next step.

Hence C15-phosphonate **2** can be generated from condensation of C14-aldehyde **9** and methylenebisphosphonic acid tetraalkyl ester **5** in the presence of NaH at 10–15 °C in 88.8% yield.

All that now remained to complete our synthesis of all-*E*-lycopene **1** was to carry out another Wittig–Horner reaction with C15-phosphonate **2** and C10-triene aldehyde **3** in the presence of KO*t*-Bu. Also 1,4,6,10-tetraene-C15-phosphonate **2** should be converted to 2,4,6,10-tetraene-C15-phosphonate carbanion **2** before condensation with C10-trienedial **3** through an analogous process as shown in Scheme 3.

But C15-phosphonate **2** from C5-aldehyde **4** after the above five-step reaction is now composed of eight isomers with three newly introduced double bonds at 1,4,6 positions (the analysis of its ^{13}C NMR spectroscopic data presented in Fig. 2), and of course various lycopene isomers will be generated if those phosphonate **2** isomers are used as the intermediates. So how to obtain all-*E*-lycopene **1** seems to be a problem. It is worthy to note that the structure of lycopene is composed of thirteen double bonds, which makes the molecule a big conjugating system and all-*E*-lycopene **1** is the most stabilizing isomer. Therefore the rearrangement of all the isomers to all-*E*-lycopene **1** is feasible, and our experimental results indicated that the complete rearrangement to all-*E*-lycopene **1** occurred by stirring the crude product for 1 h at 75–80 °C in ethanol. The ^{13}C NMR presented in Fig. 3 indicates that there are 13 peaks between δ (ppm) 120–140, which represent 26 carbons of 13 double bonds from the only isomer all-*E*-lycopene **1**.

In summary, a new route for the total synthesis of all-*E*-lycopene **1** is devised with a total yield of 26.9%, in which Wittig–Horner condensation is used as the only way in the chain-extension starting from 4,4-dimethoxy-3-methylbutanal **4**, and the intermediates C6-phosphonate **6**, dimethoxy-3,5,9-triene **8**, and C15-phosphonate **2** have not been reported before. Since all the synthetic steps are easily operated, and all of the key building blocks could be prepared in large scale, the synthetic route discussed herein may be used as a practical route for the synthesis of all-*E*-lycopene **1**.

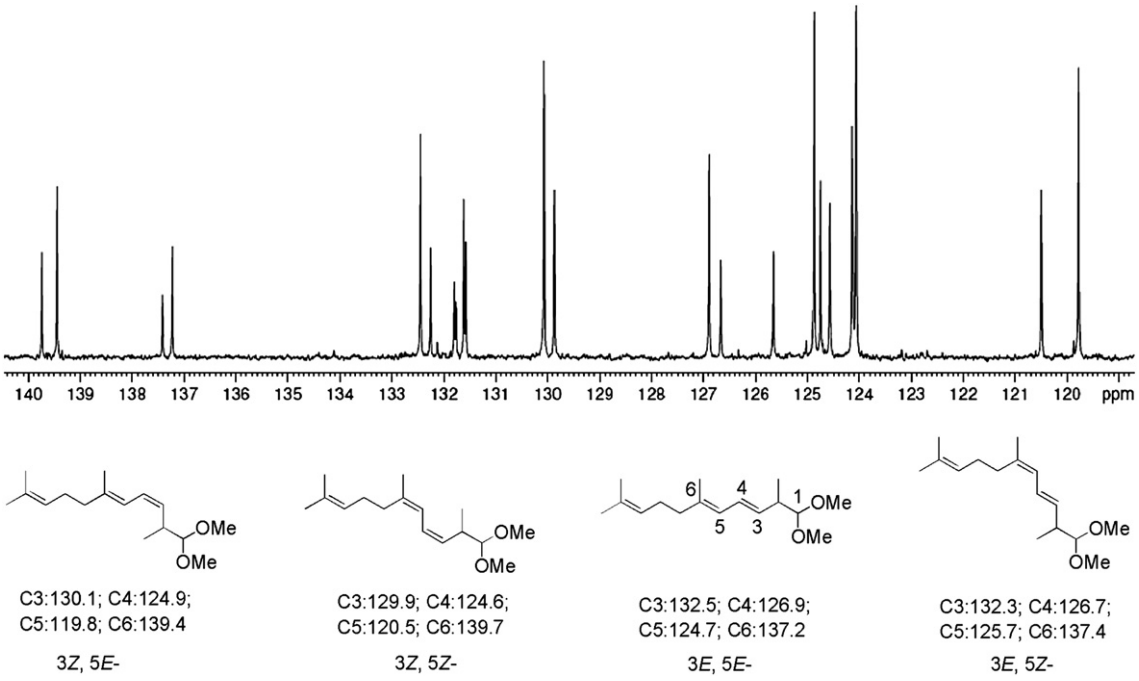


Fig. 1. Partial ^{13}C NMR spectrum (100 MHz, $CDCl_3$) and its chemical shift data for the four isomers of dimethoxy-3,5,9-triene **8**.

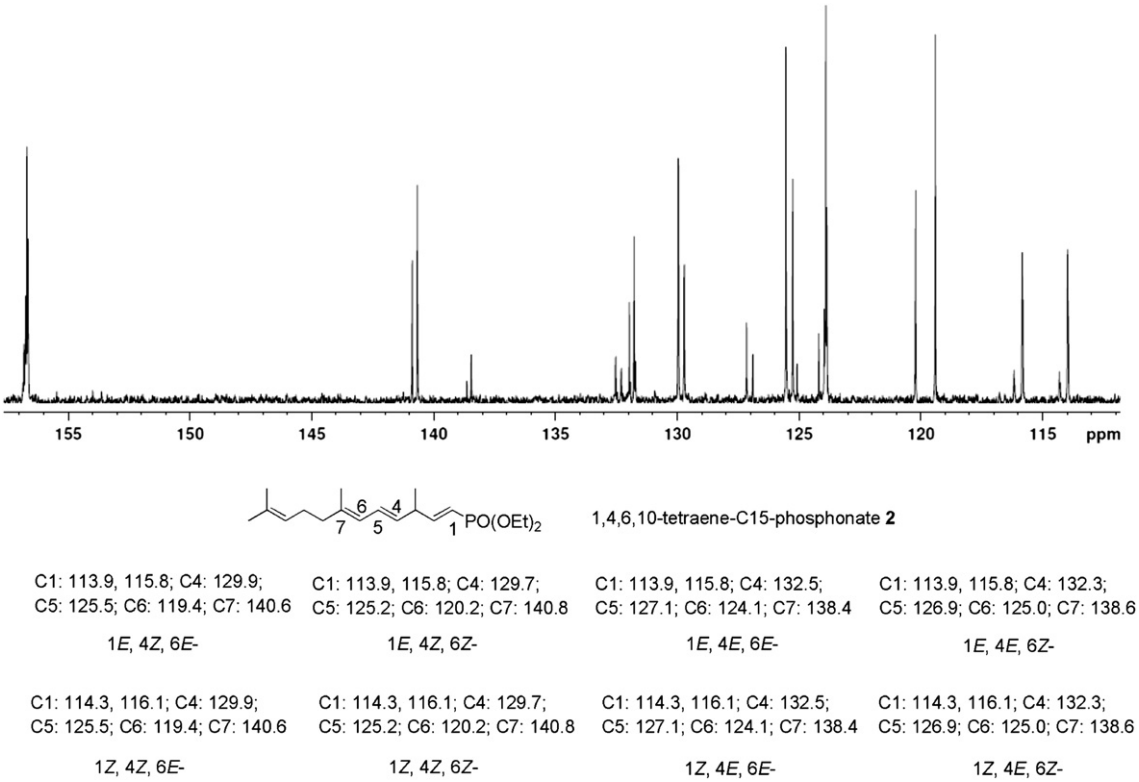


Fig. 2. Partial ^{13}C NMR spectrum (100 MHz, $CDCl_3$) and its chemical shift data for the eight isomers of 1,4,6,10-tetraene-C15-phosphonate **2**.

3. Experimental

3.1. General details

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

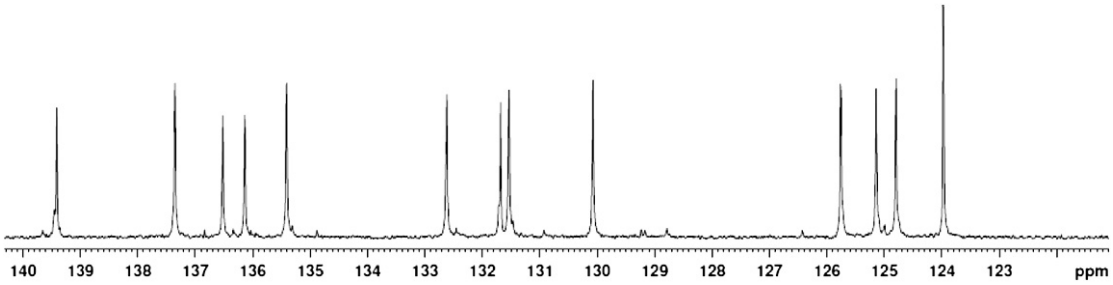


Fig. 3. Partial ^{13}C NMR spectrum (100 MHz, $CDCl_3$) and its chemical shift data for all-*E*-lycopene **1**.

3.1.1. Propenyl-C6-phosphonate ***6***. To a solution of sodium hydride (4.4 g, 60% content, 0.11 mol) in toluene (20 mL), methylenebisphosphonic acid tetraethyl ester **5** (34.5 g, 0.12 mol) in toluene (60 mL) was added dropwise at 10–15 °C over 30 min under a nitrogen atmosphere, and the resulting mixture was then stirred for 30 min. Then 4,4-dimethoxy-3-methylbutanal **4** (14.4 g, 0.1 mol) in toluene (40 mL) was added dropwise at 10–15 °C over 30 min, and the mixture was stirred for 30 min. Then water (40 mL) was added and stirred for another 10 min. The organic layer was washed with brine (10%, 40 mL), then dried over anhydrous $MgSO_4$, and evaporated in vacuo to leave 26.2 g of crude propenyl-C6-phosphonate **6** as a colorless liquid (GC content 92.2%, yield 86.9%. bp about 107–111°C/1mmHg). IR ν_{max} (neat) 1631, 1246, 1053, 1025, 967, 829 cm^{-1}; GC–MS (*m*/*z*): 279, 265, 249, 220, 205, 195, 177, 163, 149, 121, 111, 95, 81, 75 (100%), 67, 47, 29; ^1H NMR (δ, ppm, 400 MHz, $CDCl_3$): 0.92 (d, *J*=6.8 Hz, 3H, $-CHCH_3$); 1.33 (t, *J*=7.2 Hz, 6H, OCH_2CH_3); 1.91–1.97 (m, 1H, $-CHCH_3$); 2.03–2.10, 2.43–2.49 (m, m, 2H, $-CH_2$); 3.34, 3.36 (s, s, 6H, $CH(OCH_3)_2$); 4.04–4.11 (m, 4H, OCH_2CH_3); 4.05 (d, *J*=6.4 Hz, 1H, $CH(OCH_3)_2$); 5.67 (dd, *J*=16.8 Hz, 21.6 Hz, 1H, $CH{=}CHCH_2$); 6.70–6.79 (m, 1H, $CH{=}CHCH_2$); ^{13}C NMR (δ, ppm, 100 MHz, $CDCl_3$): 152.1 (d, *J*=4.6 Hz, =CH); 118.5 (d, *J*=186 Hz, =CHPO); 108.1 (s, CH); 61.6 (d, *J*=5.4 Hz, OCH_2); 54.3 (d, *J*=59 Hz, OCH_3); 36.7 (d, *J*=22.2 Hz, CH_2); 35.2 (s, CH); 16.4 (d, *J*=6.5 Hz, CH_2CH_3); 14.5 (s, CH_3); HRMS (EI^+) *m*/*z* calcd for $C_{12}H_{25}O_5P$, 280.1440, found: 280.1437.

3.1.2. Dimethoxy-3,5,9-triene ***8***. To a solution of KO*t*-Bu (9.3 g, 0.083 mol) in 8:1 (v/v) mixture of dry THF and DMSO (50 mL), propenyl-C6-phosphonate **6** (21.0 g, 0.075 mol) was added dropwise in 30 min at −30 to −25 °C under a nitrogen atmosphere, and the resulting mixture was stirred for further 1 h. Then, a few of the reaction mixture was taken out followed by hydrolyzation, and GC indicated propenyl-C6-phosphonate **6** had been converted to allylic-C6-phosphonate **10** completely, which is a mixture of *Z*- and *E*-isomers of same spectroscopic data according to GC–MS. A sample of the above rearrangement product was identified as follow: GC–MS (*m*/*z*): 279, 265, 249, 233, 220, 205, 189, 177, 161, 152, 138, 125, 111, 97, 81, 75 (100%), 67, 47, 29.

Then, 6-methyl-5-hepten-2-one **7** (9.5 g, 0.075 mol) was added to the above mixture dropwise at −30 to −25 °C over 1 h. The mixture was warmed to room temperature and the stirring was continued for another 30 min. Then, water (50 mL) and ether (100 mL) were added, and the ether phase was separated, washed with brine (10%, 3×15 mL), dried over anhydrous $MgSO_4$, and evaporated in vacuo to collect the distillate at 99–103 °C/1mmHg as a colorless liquid (14.1 g). GC and NMR showed the liquid consisted of the mixture of 3*E*,5*Z*-; 3*Z*,5*Z*-; 3*E*,5*E*-; 3*Z*,5*E*-(major product) four isomers of dimethoxy-3,5,9-triene **8** with the ratio of about 1:2:2:4 (total GC content of the four isomers 87.5%, yield 65.3%).

The spectral data of only 3*Z*,5*E*-(major product) are presented as follow: GC–MS (*m*/*z*): 252, 220, 192 (100%), 178, 165, 152, 115, 102, 91, 77, 65, 51, 39; ^1H NMR (δ, ppm, 400 MHz, $CDCl_3$): 1.00 (d, *J*=6.8 Hz, 3H, $CHCH_3$); 1.61 (s, 3H, $=CCH_3$); 1.68 (s, 3H, $=CCH_3$); 1.75 (s, 3H, $=CCH_3$); 2.04–2.18 (m, 4H, CH_2CH_2); 2.93–2.97 (m, 1H, $CHCH_3$); 3.378, 3.381 (s, s, 6H, $CH(OCH_3)_2$); 4.12–4.14 (m, 1H, $CH(OCH_3)_2$); 5.10–5.13 (m, 1H, =C*H*); 5.19–5.27 (q, *J*=10.4 Hz, 1H, =C*H*); 6.06 (d, *J*=11.2 Hz, 1H, =C*H*); 6.19–6.25 (m, 1H, =C*H*); ^{13}C NMR (δ, ppm, 100 MHz, $CDCl_3$): 139.4 (=C); 131.6 (=C); 130.1 (=CH); 124.9 (=CH); 124.1 (=CH); 119.8 (=CH); 108.2 (CH); 53.6 (CH_3); 40.3 (CH_2); 35.3 (CH); 26.6 (CH_2); 25.7 (CH_3); 17.7 (CH_3); 16.5 (CH_3); 16.2 (CH_3); DEPT135: 139.4; 131.6; 130.1; 124.9; 124.1; 119.8; 108.2; 53.6; 40.3 (D); 35.3; 26.6 (D); 25.7; 17.7; 16.5; 16.2; HRMS (EI^+) *m*/*z* calcd for $C_{16}H_{28}O_2$, 252.2089, found: 252.2087.

3.1.3. C14-Aldehyde ***9***. Dimethoxy-3,5,9-triene **8** (12.6 g, 0.05 mol), THF (100 mL), *p*-TSA (1.5 g), and water (22 g) were added into a 3-neck reaction flask under a nitrogen atmosphere, then the resulting mixture was stirred at 20–25 °C for 24 h. When the hydrolysis finished completely (GC), aqueous $NaHCO_3$ (9%, 20 mL) was added, and THF was removed under reduced pressure. Then cyclohexane (100 mL) was added and the organic layer was washed with water (30 mL), then dried, and evaporated in vacuo to leave the crude C14-aldehyde **9** (10.5 g, GC content 85.1%, yield 86.8%), which were composed of four isomers same as the stereochemistry of raw material dimethoxy-3,5,9-triene **8**, the spectra data of 3*Z*,5*E*-(major product) are presented as follow: GC–MS (*m*/*z*): 206, 191, 163, 135, 121, 109, 95 (100%), 69, 55, 41; ^1H NMR (δ, ppm, 400 MHz, $CDCl_3$): 1.19–1.21 (m, 3H, $CHCH_3$); 1.43 (s, 3H, $=CCH_3$); 1.61 (s, 3H, $=CCH_3$); 1.69 (s, 3H, $=CCH_3$); 1.75–1.87 (m, 2H, $=CHCH_2$); 2.09–2.13 (m, 2H, $=CCH_2$), 3.46–3.56 (m, 1H, $CHCH_3$), 5.09–5.10 (m, 1H, =CH), 5.10–5.16 (m, 1H, =CH), 6.06 (d, *J*=9.6 Hz, 1H, =CH), 6.45 (t, *J*=9.6 Hz, 1H, =CH), 9.54 (s, 1H, −CHO); ^{13}C NMR (δ, ppm, 100 MHz, $CDCl_3$): 201.0 (CHO); 142.1 (=C); 128.6 (=CH); 124.0 (=CH); 123.8 (=CH); 123.6 (=C); 119.3 (=CH); 45.9 (CH); 40.3 (CH_2); 26.9 (CH_2); 25.7 (CH_3); 17.7 (CH_3); 16.7 (CH_3); 14.0 (CH_3); DEPT135: 201.0; 128.6; 124.0; 123.8; 119.3; 45.9; 40.3 (D); 26.9 (D); 25.7; 17.7; 16.7; 14.0.

3.1.4. C15-Phosphonate ***2***. To a solution of sodium hydride (2.2 g, 60% content, 0.055 mol) in toluene (20 mL), a solution of methylenebisphosphonic acid tetraethyl ester (17.3 g, 0.06 mol) in toluene (40 mL) was added dropwise at 10–15 °C over 30 min under a nitrogen atmosphere, and the resulting mixture was then stirred for additional 30 min. Then C14-aldehyde **9** (10.3 g, 0.05 mol) in toluene (20 mL) was added dropwise at 10–15 °C over 30 min, and the mixture was stirred for further 30 min. Then water (50 mL) was added and stirred for further 10 min. The organic layer was washed with aqueous NaCl (10%, 50 mL), dried over anhydrous $MgSO_4$, and evaporated in vacuo to leave crude product 3,7,11-trimethyl-1,4,6,10-dodecatetraenylphosphonic acid diethyl ester **2** (15.1 g, GC content 93.2%, yield 88.8%) as a pale brown liquid. The spectra data of 1*E*,3*Z*,5*E*-(major product) are presented as follow: GC–MS (*m*/*z*): 340, 325, 297, 284, 271, 257, 243, 232, 217, 205, 192, 178, 164, 146, 133 (100%), 119, 105, 91, 79, 69, 55, 41; ^1H NMR (δ, ppm, 400 MHz, $CDCl_3$): 6.74 (t, *J*=19.6 Hz, 1H, =C*H*); 6.24 (t, *J*=11.2 Hz, 1H, =C*H*); 6.00 (d, *J*=11.6 Hz, 1H, =C*H*); 5.63 (t, *J*=19.2 Hz, 1H, =C*H*PO),

5.06–5.14 (m, 2H, =C*H*, =C*H*); 4.02–4.10 (m, 4H, PO(CH_2CH_3)$_2$); 3.43–3.53 (m, 1H, C*H*CH_3); 2.06–2.15 (m, 4H, CH_2CH_2); 1.83 and 1.80 (s, 3H, =CCH_3); 1.69 (s, 3H, =CCH_3); 1.61 (s, 3H, =CCH_3); 1.31 (t, J=7.2 Hz, 6H, PO(CH_2CH_3)$_2$); 1.15 (d, J=6.8 Hz, 3H, CHCH_3); ^{13}C NMR (δ, ppm, 100 MHz, $CDCl_3$): 156.7 (s, =CH); 140.6 (s, =C); 131.7 (s, =C); 129.9 (s, =CH); 125.5 (s, =CH); 123.9 (s, =CH); 119.4 (s, =CH); 114.9 (d, J=186.4 Hz, =CHPO); 61.6 (d, J=5.5 Hz, OCH_2CH_3); 40.3 (s, CH_2); 36.1 (d, J=21.1 Hz, CH); 26.6 (s, CH_2); 25.7 (s, CH_3); 19.7 (s, CH_3); 17.7 (d, J=2.7 Hz, CH_3); 16.9 (s, CH_3); 16.3 (d, CH_3); DEPT135: 156.7; 129.9; 125.5; 123.9; 119.4; 115.8 and 113.9; 61.63 (D), 61.67 (D); 40.3 (D); 36.2 and 36.0; 26.6 (D); 25.7; 19.7; 17.7 and 17.6; 16.9; 16.34 and 16.28; HRMS (EI$^+$) m/z calcd for $C_{19}H_{33}O_3P$, 340.2167, found: 340.2170.

3.1.5. All-E-lycopene ***1****.* To a solution of KO*t*-Bu (2.3 g, 0.021 mol) in 8:1 (v/v) mixture of dry THF and DMSO (30 mL), C15-phosphonate **2** (6.8 g, 0.02 mol) was added dropwise at −30 to −25 °C over 30 min under a nitrogen atmosphere, and the resulting mixture was stirred for further 2 h, C10-triene dialdehyde **3** (1.6 g, 0.0098 mol) in 8:1 (v/v) mixture of dry THF and DMSO (10 mL) was added dropwise over 20 min, and the mixture was stirred for another 15 min at −30 to −25 °C, then stirred for further 1 h at 20–25 °C. Then $CHCl_3$ (100 mL) was added and the organic layer was separated, washed with aqueous NaCl (5%, 3×75 mL), dried over anhydrous $MgSO_4$, and evaporated in vacuo to leave crude product as a red solid, which can be further recrystallized using CH_2Cl_2 (30 mL) and then the solid product stirred for 1 h at 75–80 °C in 30 mL ethanol to finish rearrangement and pure product obtained (3.3 g, 61.6%). The identity was confirmed by IR and NMR analysis. IR ν_{max} (neat) 1627, 968 cm^{-1}; ^{1}H NMR (δ, ppm, 400 MHz, $CDCl_3$): δ 5.11, 5.98–6.94 (m, 16H, =CH); 1.55 (s, 12H, 4× CH_3), 1.62 (s, 6H, 2× CH_3), 1.69 (s, 6H, 2× CH_3), 2.13 (s, 6H, 2× CH_3); 1.43–2.21 (m, 8H); ^{13}C NMR (δ, ppm, 100 MHz, $CDCl_3$): 139.5 (s, =C); 137.4 (s, CH); 136.6 (s, =C); 136.2 (s, =C); 135.4 (s, =CH); 132.7 (s, =CH); 131.8 (s, =C); 131.6 (s, =CH); 130.1 (s, =CH); 125.7 (s, =CH); 125.2 (s, =CH); 124.8 (s, =CH); 124.0 (s, =CH); 40.3 (s, CH_2); 26.7 (s, CH_2); 25.7 (s, CH_3); 18.4 (s, CH_3); 17.0 (s, CH_3); 12.9 (s, CH_3); 12.8 (s, CH_3). There are 13 peaks between δ (ppm) 120–140 and seven peaks between δ (ppm) 10–45, which indicate all-trans structure and high purity. DEPT135: 137.4; 135.4; 132.7; 131.6; 130.1; 125.7; 125.2; 124.8; 124.0; 58.5 (D); 40.3 (D); 26.7 (D); 25.7; 18.4; 17.0; 12.9; 12.8.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.05.104. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

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