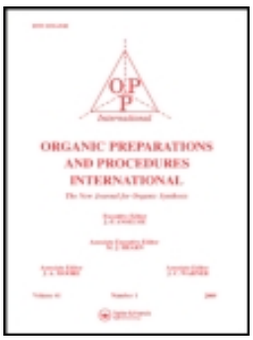


Taylor & Francis
Taylor & Francis Group

Organic Preparations and Procedures International

The New Journal for Organic Synthesis

ISSN: 0030-4948 (Print) 1945-5453 (Online) Journal homepage: http://www.tandfonline.com/loi/uopp20

Practical Synthesis of Lycopene

Xiaohua Song, Huiting Xu, Weidong Ye, Chunlei Lv, Ruiwei Cao, Chunlei Wu & Runpu Shen

To cite this article: Xiaohua Song, Huiting Xu, Weidong Ye, Chunlei Lv, Ruiwei Cao, Chunlei Wu & Runpu Shen (2016) Practical Synthesis of Lycopene, Organic Preparations and Procedures International, 48:4, 350-354, DOI: 10.1080/00304948.2016.1194133

To link to this article: http://dx.doi.org/10.1080/00304948.2016.1194133

Organic Preparations and Procedures International, 48:350–354, 2016

ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2016.1194133

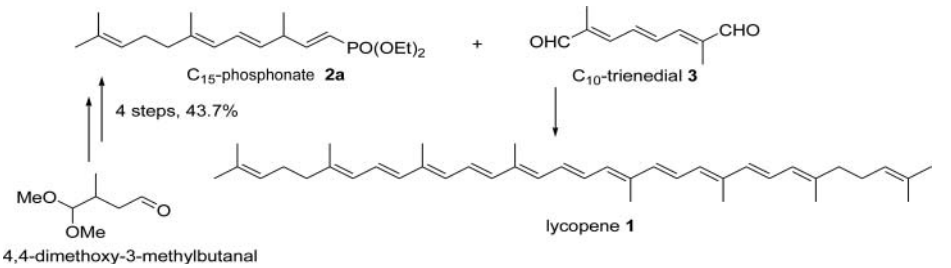
Practical Synthesis of Lycopene

Xiaohua Song,[1] Huiting Xu,[1] Weidong Ye,[2] Chunlei Lv,[2] Ruiwei Cao,[2] Chunlei Wu,[1] and Runpu Shen[1]

[1]Department of Chemistry and Chemical Engineering, Shaoxing University, Shaoxing, Zhejiang 312000, P. R. of China
[2]Zhejiang Medicine Co. Ltd., Shaoxing, Zhejiang, 312000, P. R. of China

Carotenoids are a large group of lipid-soluble pigments biosynthesized in plants, in bacteria, in some fungi and in algae.[1,2] Lycopene is a red pigmented carotenoid found in tomatoes. It contains thirteen double bonds and has a greater radical scavenging ability than β-carotene. It has shown potential as protection against a variety of serious disorders such as some cancers, cardiovascular and degenerative eye diseases.[3-6] These interesting biological properties as well as its unique molecular structure have stimulated a number of efforts to produce lycopene[7-15] since its first reported synthesis in 1950,[16] whose the major goal was the design of a method to introduce newly conjugated carbon-carbon double bonds.

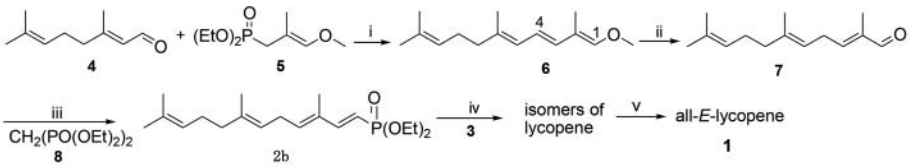
We previously reported a practical route for the total synthesis of lycopene *via* a stepwise C15 + C10 + C15 double Wittig-Horner reaction,[17] in which C_{15}-phosphonate **2a** was prepared as the key building blocks starting from 4,4-dimethoxy-3-methylbutanal (*Scheme 1*).



Scheme 1

More recently, we designed a new synthetic route to ε-carotene from α-cyclocitral and diethyl (3-methoxy-2-methylprop-2-en-1-yl)phosphonate **5**.[18] The present article describes a three-step route to C_{15}-phosphonate **2b** from citral (**4**) and compound **5**; compound **2b** was then coupled with C_{10}-trienedial **3** to give lycopene (*Scheme 2*).

Received February 3, 2016; in final form May 7, 2016.
Address correspondence to Chunlei Wu, Department of Chemistry and Chemical Engineering, Shaoxing University, Shaoxing, Zhejiang 312000, P. R. of China. E-mail: wuchunlei2006@usx.edu.cn



Reagents and conditions: (i) KOt-Bu, THF and DMSO, -30 to -25°C, 68%; (ii) p-TSA, THF and water, 20 to 25°C, 88%; (iii) NaH, toluene, 10 to 15°C, 89%; (iv) NaOt-Bu, THF and DMSO, 20 to 25°C, 59%; (v) ethanol, 75 to 80°C.

Scheme 2

Condensation of citral (**4**) with diethyl (3-methoxy-2-methylallyl)phosphonate **5**, prepared according to a literature procedure [19] in the presence of potassium *tert*-butoxide at −30 to −20°C gave the C_{14}-enol ether **6** in 68% yield as a colorless liquid which was purified by distillation. The product was mainly composed of 1*E*, 4*Z*-; 1*Z*, 4*Z*-; 1*E*, 4*E*-; 1*Z*, 4*E*- four isomers in a ratio of about 1:1:1:1 according to the analysis of its NMR spectrum. The mixture of the four isomers was used without separation in the next step.

The C_{14}-enol ether **6** was then readily converted into the corresponding C_{14}-aldehyde **7** in the presence of *p*-toluenesulfonic acid in 83% yield; during this step, the double bonds at carbon 3 isomerized to carbon 2 to produce conjugated aldehyde **7**. Then C_{15}-phosphonate **2b** was obtained in 89% yield by condensation of **7** with tetraethyl methylene*bis*phosphonate **8** in the presence of sodium hydride at 10 to 15°C. The final step to complete the synthesis of lycopene **1** involves a second Wittig–Horner reaction of the C_{15}-phosphonate **2b** with the C_{10}-trienedial **3** in the presence of sodium *tert*-butoxide; However, to obtain the structure of lycopene **1**, the required conversion of 1,3-diene-C_{15}-phosphonate **2b** to the corresponding 2,4-diene-C_{15}-phosphonate **2** prior to condensation with the C_{10}-trienedial **3** (*Scheme 3*) occurred *in situ* under these conditions.[7]

Scheme 3

The lycopene obtained in the present study was composed of at least four isomers and the use of our previously reported procedure[5] led to complete isomerization to all-*E*-lycopene as indicated by stirring the crude product for 1 h at 75–80°C in ethanol as indicated by the NMR spectrum.

In summary, a new route has been developed for the total synthesis of lycopene with an overall yield of 31% from readily available citral ***4***, in which a Wittig–Horner condensation was used as the sole method for chain extension. Because all the steps are readily performed and all the key building blocks can be prepared on a large scale, the route described here should be useful as a practical route for the synthesis of lycopene.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DMX II I400M spectrometer. Samples were dissolved in $CDCl_3$, which served as the deuterium lock for the

spectrometers. TMS and residual $CHCl_3$ were 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. Citral **4**, methylene-*bis*phosphonic acid tetraethyl ester **8**, and C_{10}-trienedial **3** were supplied by Zhejiang Medicine Co. Ltd..

1-Methoxy-2,6,10-Trimethylundeca-1,3,5,9-tetraene (6)

To a solution of KO*t*-Bu (12.3 g, 0.11 mol) in 8:1 (v/v) mixture of dry THF and DMSO (50 mL), phosphonate **5** (22.2 g, 0.1 mol) was added dropwise over 30 minutes at −30 to −20°C under N_2 and the mixture was stirred at that temperature for 1 h. Then a solution of citral **4** (15.2 g, 0.1 mol) in 8:1 (v/v) mixture of dry THF and DMSO (10 mL) was added dropwise over 1 h. The mixture was stirred for another 30 min until the reaction was complete (GC). Water (50 mL) and diethyl ether (100 mL) were added, and the mixture was stirred for another 10 min. The organic layer was separated, washed with 5% aqueous NaCl (5%, 3 × 25 mL), dried ($MgSO_4$), and evaporated *in vacuo* to leave 16.1 g (68%) of crude C_{14}-enol ether **6** as a colorless liquid (composed of four isomers) (GC content 93.5%)

IR (film): 3120, 1683, 1657, 1250 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 3H, $CH_3C=CHOCH_3$), 1.68 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.78 (s, 3H, $CH=CCH_3$), 2.05-2.17 (m, 4H, CH_2CH_2), 3.62 (s, 3H, OCH_3), 5.06–5.16 (m, 1H, CH), 5.87 (s, 1H, $C=CHOCH_3$), 5.94 (dd, J = 11.2 Hz, 5.6 Hz, 1H, $CH=CH$), 6.29 (dd, J = 15.2 Hz, 11.2 Hz, 1H, $C=CH$), 6.63 (dd, J = 15.2 Hz, 12.4Hz, 1H, $CH=CH$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 17.7, 24.0, 25.7, 26.6, 26.8, 32.7, 40.1, 59.8, 112.8, 123.2, 126.7, 129.0, 138.0, 144.8. ^{13}C DEPT135 (100 MHz, $CDCl_3$): δ 14.5, 17.7, 24.0, 25.7, 26.6 (−), 26.8 (−), 32.7 (−), 40.1 (−), 59.8, 123.2, 126.7, 144.8. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{15}H_{24}O$: 220.1827. Found: 220.1823.

2,6,10-Trimethylundeca-2,5,9-trienal (7)

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 to 25°C for 24 h. When hydrolysis was complete (GC), 9% aqueous $NaHCO_3$ (20 mL) was added and the THF was removed under reduced pressure. Cyclohexane (100 mL) was added and the organic layer was separated, washed with H_2O (30 mL), dried, and concentrated *in vacuo* to give 9.1 g (88%) of crude product (GC content 93.1%) as a pale yellow liquid.

^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, J = 7.6 Hz, 3H, CH_3CCHO), 1.51 (s, 3H, $CH_3C=CH$), 1.63 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.85–1.89 (m, 2H, CH_2CH_2), 2.18–2.29 (m, 2H, CH_2CH_2), 2.24–2.33 (m, 2H, CH_2), 5.11–5.12 (m, 1H, CH), 5.67 (s, 1H, $CH_3C=CH$), 6.51 (t, J = 7.2 Hz, 1H, $CH=CCHO$), 9.44 (s, 1H, CHO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.7, 17.6, 18.3, 23.4, 25.6, 26.4, 39.4, 115.5, 123.9, 131.6, 140.7, 143.0, 156.8, 194.4. ^{13}C DEPT135 (100 MHz, $CDCl_3$): δ 12.7, 17.6, 18.3, 23.4 (−), 25.6, 26.4 (−), 39.4 (−), 115.5, 123.9, 156.8, 194.4. GC-MS: m/z (%) = 206, 191, 177, 163, 109, 91, 77, 69(100%), 53, 41, 27. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{14}H_{22}O$: 206.1671; Found:206.1673.

Diethyl (3,7,11-trimethyldodeca-1,3,6,10-Tetraenyl)phosphonate (2b)

A solution of tetraethyl methylene*bis*-phosphonate (**8**, 8.6 g, 0.03 mol) in toluene (20 mL) was added dropwise over 30 min to a solution of 1.1 g of NaH (60% in oil,

0.028 mol) in toluene (10 mL) at 10 to 15°C under nitrogen, and the mixture was stirred for 30 min. Then a solution of aldehyde **7** (5.1 g, 0.025 mol) in toluene (20 mL) was added dropwise over 30 min at 10 to15°C, and the mixture was stirred for a further 30 min. Water (20 mL) was added and the mixture was stirred for 10 min. The organic layer was separated, washed with 10% aq NaCl (80 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product (GC content 93.2%) as a pale-brown liquid; yield: 7.5 g (89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, J = 7.6 Hz, 3H, CH_3), 1.32 (t, J = 6.8 Hz, 6H, 2 × OCH_2CH_3), 1.46 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.96-2.04 (m, 2H, CH_2CH_2), 2.04-2.14 (m, 2H, CH_2CH_2), 2.15–2.20 (m, 2H, CH_2), 4.03-4.10 (m, 4H, 2 × OCH_2CH_3), 5.10-5.11 (m, 1H, CH), 5.55–5.56 (m, 1H, CH), 5.51 (dd, J = 16.8 Hz, 20.0 Hz, 1H, CH = C*H*P), 5.86 (t, J = 7.2 Hz, 1H, CH), 7.08 (dd, J = 17.6 Hz, 21.6 Hz, 1H, C*H* = CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 15.9, 16.0, 17.0, 17.3, 22.7, 25.3, 25.9, 38.6, 61.0, 60.9, 112.4 (d, J = 189.4 Hz), 118.2, 123.7, 131.2, 135.5 (d, J = 24.1 Hz), 141.0, 142.7, 151.3. ^{13}C DEPT135 (100 MHz, $CDCl_3$): δ 12.8, 15.9, 16.0, 17.0, 17.3, 22.7 (−), 25.3, 25.9 (−), 38.6 (−), 61.0 (−), 60.9 (−), 112.4 (d, J = 189.4 Hz), 118.2, 123.7, 142.7, 151.3. GC-MS: m/z (%) = 340, 325, 284, 271, 243, 217(100%), 205, 192, 159, 105, 79. HRMS (ESI): m/z $[M + H]^+$ Calcd for $C_{19}H_{33}O_3P$: 340.2167; Found: 340.2170.

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), C_{15}-phosphonate **2b** (6.8 g, 0.02 mol) was added dropwise at −30 to −25°C over 30 min under N_2, and the resulting mixture was stirred for further 5 h at that temperature. Then, C_{10}-trienedial **3** (1.6 g, 0.0098 mol) in 8:1 (v/v) THF and DMSO (10 mL) was added dropwise over 20 min. The mixture was stirred for 15 min at −30 to −25°C, and then stirred for further 1 h at 20 to 25°C. Chloroform (100 mL) was added and the organic layer was separated, washed with aqueous 5% NaCl (3 × 75 mL), dried ($MgSO_4$), and evaporated *in vacuo* to leave crude product as a red solid, which was recrystallized from CH_2Cl_2 (30 mL) and then the solid product stirred for 1 h at 75 to 80°C in 30 mL ethanol to complete the isomerization to afford pure product (3.1 g, 59%), as a red solid, mp. 170–171°C, lit.[20] mp. 171°C. Its identity was confirmed by IR and NMR analysis.

IR (film): 1627, 968 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 6H, 2 × CH_3), 1.69 (s, 6H, 2 × CH_3), 1.82 (s, 6H, 2 × CH_3), 1.97 (s, 12H, 4 × CH_3), 2.20-2.23 (m, 8H, 4 × CH_2), 5.11 (t, 2H, 2 × C*H*CH_2), 5.95 (d, 2H, 2 × C*H*CH), 6.19 (d, 2H, 2 × C*H*CH), 6.27 (d, 4H, 4 × C*H*CH), 6.35 (d, 2H, 2 × C*H*CH), 6.52 (t, 2H, 2 × C*H*CH), 6.63 (m, 4H, CHC*H*CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 12.9, 17.0, 17.7, 25.7, 26.7, 40.2, 124.0, 124.8, 125.2, 125.7, 130.1, 131.6, 131.7, 132.6, 135.4, 136.2, 136.5, 137.4, 139.5. ^{13}C DEPT135 (100 MHz, $CDCl_3$): δ 12.8, 12.9, 17.0, 17.7, 25.7, 26.7 (−), 40.2 (−), 124.0, 124.8, 125.2, 125.7, 130.1, 131.6, 132.7, 135.4, 137.4. HRMS (ESI): m/z $[M + H]^+$ Calcd for $C_{40}H_{56}$: 536.8726; Found: 536.8724.

Acknowledgments

We acknowledge the National Natural Science Foundation of China (No. 21176156), Public Projects of Zhejiang Province of China (No. 2016C31032) and Research Fund of Zhejiang Educational Committee of China (Y 201431839).

References

1. J. A. Maresca, J. E. Graham and D. A. Bryant, *Photosynth. Res.*, **97**, 121 (2008).
2. Cazzonelli and I Christopher, *Funct. Plant Biol.*, **38**, 833 (2011).
3. L. Joseph, B. Emili, F. Bianca and G. Yudit, *Nutr. Cancer*, **24**, 257 (1995).
4. G. Edward, A. Alberto, B. R. Eric, J. S. Meir, A. C. Graham and C. W. Walter, *J. Natl. Cancer Inst.*, **87**, 1767 (1995).
5. F. Khachik, J. S. Bertram, M.-T. Huyang, J. W. Fahey and P. Talalay, *Antioxidant Food Supplements in Human Health: Packer L., Hiramatsu M., Yoshikawa T; Academic Press: San Diego, Chap*, **14**, 203 (1999).
6. X. Zhang, W. Zhao, L. Hu, L. Zhao and J. Huang, *Arch. Biochem. Biophys.*, **512**, 96 (2011).
7. P. S. Manchandr, R. Rüegg, U. Schwieter, P. T. Siddons and B. C. L. Weedon, *J. Chem. Soc.* 2019 (1965).
8. H. Bienaymé, *Tetrahedron Lett.*, **35**, 6867 (1994).
9. J. H. Babler, Harvey, W. WO 2000031086, 2000; *Chem. Abstr.*, **131**, 310747 (2000).
10. H. Ernst, *Pure Appl. Chem.*, **74**, 2213 (2002).
11. S. K. Guha and S. Koo, *J. Org. Chem.*, **70**, 9662 (2005).
12. G. Pattenden and D. C. Robson, *Tetrahedron*, **62**, 7477 (2006).
13. A. Valla, B. Valla, R. Le Guillou, D. Cartier, L. Dufossé, and R. Labia, *Helv. Chim. Acta.*, **90**, 512 (2007).
14. N. Fontán, B. Vaz, R. Álvarez and Á. R. de Lera, *Chem. Commun.*, **49**, 2694 (2013).
15. K. Crawford, E. Mazzola and F. Khachik, *Synthesis*, **46**, 635 (2014).
16. P. Karrer and C. H. Eugster, *Helv. Chim. Acta.*, **33**, 1349 (1950).
17. R. Shen, X. Jiang, W. Ye, X. Song, L. Liu, X. Lao and C. Wu, *Tetrahedron*, **67**, 5610 (2011).
18. C. Wu, R. Cao, X. Song, C. Lv, W. Ye, S. Pi, C. Chen and R. Shen, *Synthesis*, **47**, 481 (2015).
19. G. Lavielle, *Bull. Soc. Chim. Fr.*, **11**, 4186 (1967).
20. J. D. Surmatis and A. Ofner, *J. Org. Chem.*, **28**, 2735 (1963).