Journal of the Iranian Chemical Society
https://doi.org/10.1007/s13738-019-01784-2

ORIGINAL PAPER

Practical synthesis of canthaxanthin

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Received: 9 April 2019 / Accepted: 24 September 2019

Abstract
In this study, a novel route for the total synthesis of canthaxanthin is described. The synthesis is firstly based on an epoxidation of α-ionone with metachloroperbenzoic acid to afford the epoxide, followed by conversion of the epoxide to 3-hydroxyl-β-ionone in the presence of sodium methoxide. Next, 3-hydroxyl-C14-aldehyde was obtained by a Darzens condensation with 4-hydroxyl-β-ionone and methyl chloroacetate, which can be converted to 3-hydroxyl-C15-phophonate via a Wittig–Horner condensation with tetraethyl methylenebisphosphonate. Then, a Wittig–Horner condensation with 3-hydroxyl-C15-phosphonate and C10-trienedial resulted in 4,4′-dihydroxyl-β-carotene, followed by an oxidation afforded the target product canthaxanthin. The overall yield of this route is 37% from α-ionone. The synthetic steps are easily operated and are practical for the large-scale production.

Keywords Canthaxanthin · Wittig–Horner condensation · Total synthesis · Phosphonate

Introduction

Canthaxanthin, one of 10 marketed commercially carotenoids, is a diketo-carotenoid with nine conjugated carbon–carbon double bonds at the center of the molecule [1]. It appears as a red–orange lipophilic pigment [2], biosynthesized in some bacteria, fungi and algae and widely used in poultry as a feed additive [3, 4]. Furthermore, it exhibits several potential health benefits, such as free radical scavenging properties, immune modulating activities and an induction of gap junction communication [1]. These interesting biological properties as well as its unique molecular structure have stimulated a number of efforts to produce canthaxanthin since the first synthesis in 1958 [5], in which the most concern is how to introduce newly conjugated carbon–carbon double bonds. Undoubtedly, Wittig-type condensation is the main shortcut for this purpose [6–8]. The most representative disconnection of canthaxanthin based on the available C15 Wittig salts and the C10-triene dialdehyde building blocks is shown in Scheme 1, in which a major disadvantage is the formation of triphenylphosphine oxide during the Wittig olefination [9–12].

Barbler has firstly reported the use of the key intermediate C15 Wittig–Horner salts, instead of C15 Wittig salts to synthesize of canthaxanthin, which can avoid the difficulties associated with the use of phosphonium salts (for example, the separation of triphenylphosphine oxide from the products) [13]. But the reaction conditions for the key intermediate allenic phosphonate in Babler's route are too rigorous and its subsequent partial hydrogenation was somewhat too difficult to finish with high selectivity. And our team has developed new strategies for the synthesis of β-carotene [14], lycopene [15, 16] and ε-carotene [17] employed C15-Wittig–Horner salts as the key intermediates.

In this paper, we report a practical approach for the synthesis of canthaxanthin by an oxidation of 4,4′-dihydroxyl-β-carotene, which was from the condensation of C15-phosphonate **2** and C10-trienedial **3**. The key intermediate C15-phosphonate **2** could be synthesized in four steps employed α-ionone as the starting material (Scheme 2).

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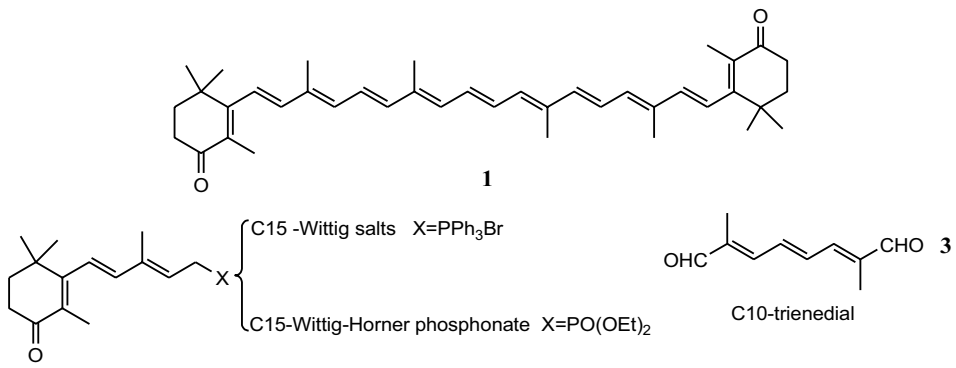
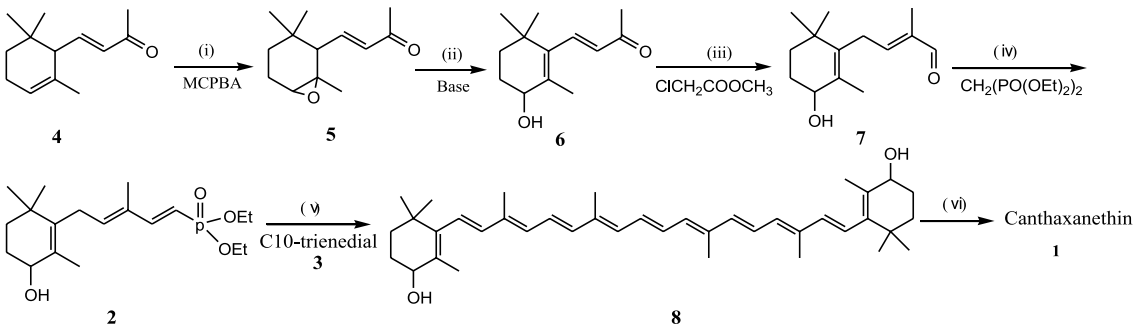
Published online: 30 September 2019

Scheme 1 C15 + C10 + C15 disconnection of canthaxanthin via Wittig reaction or Wittig–Horner reaction



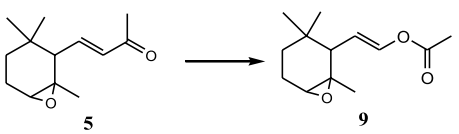


Scheme 2 Reagents and conditions: (i) MCPBA, CH_2Cl_2, 0–5 °C, 95%; (ii) sodium methoxide, CH_3OH, refluxing, 85%; (iii) sodium methoxide, toluene, −20 to 10 °C, 83%; (iv) NaOEt, ethanol, 25 °C, 93%; (v) KO*t*-Bu, THF and HMPT, −25 to −15 °C, 68%; (vi) aluminum isopropoxide, acetone, refluxing, 88%

Results and discussion

Firstly, according to the literature [18], α-ionone **4** was epoxidated with MCPBA to afford a mixture of epoxides **5**, in which one isomer predominates about 92%. The reaction should be quenched when the material α-ionone disappeared by GC, or a by-product will be formed. The structure of this impurity is a Baeyer–Villiger reaction substance **9** according to its GC–MS (Scheme 3).

Then, the above epoxide was converted to 4-hydroxyl-β-ionone **6** via isomerization in the presence of sodium methoxide. The by-product diketone was about 6% (GC), which is consistent with the literature [18], and the other by-product dehydrate was also verified according to GC–MS with about 1–2% ratio (GC). The crude product can be chromatographed on silica gel to remove the impurities according to the literature [18], which is not suitable for large-scale production. Here, we found a new methodology to purify the crude 4-hydroxyl-β-ionone. It was reacted with succinic anhydride to afford the corresponding ester, which then was dissolved in a basic aqueous solution and the impurities can be separated by extraction with water insoluble solvent. The ester was then alcoholysis by methanol in the presence of sodium methoxide to afford pure 4-hydroxyl-β-ionone **6** in 85% yield with 98% content (GC).



Scheme 3 Over-oxidation of α-ionone

Next, a Darzens reaction was carried out with 4-hydroxyl-β-ionone **6** and methyl chloroacetate. During the process, 40% sodium methoxide was added dropwise into the reaction mixture of 4-hydroxyl-β-ionone and methyl chloroacetate at −20 °C, and then, another 3-h stirring at −10 °C was needed until the spot of 4-hydroxyl-β-ionone disappeared by TLC. Then, decarboxylation was carried out at 40 °C for 30–40 min. But the TLC showed no mainly product formed. We then found the product 3-hydroxyl-C14-aldehyde **7** is very sensitive to base. In fact, the decarboxylation has been finished after 3-h stirring at −10 °C and 3-hydroxyl-C14-aldehyde **7** will be destroyed by the base at 40 °C. So when 4-hydroxyl-β-ionone disappeared, tenfold water was added to quench the reaction, and then, toluene was added to extract the crude product 4-hydroxyl-C14-aldehyde **7** to

avoid hydrolysis. The yield of the crude product was 85% with 90% content (GC), which can be raised to 94% by distillation in vacuo.

A Wittig condensation between 3-hydroxyl-C14-aldehyde **7** and tetraethyl methylenebisphosphonate was carried out in the presence of a base to afford 3-hydroxyl-C15-phosphonate **2**. During the process, NaH was used to promote the reaction, but the result 3-hydroxyl-C15-phosphonate **2** was presented as a pasty and difficult to handle. Then, we found that sodium ethoxide used as the base catalyst can resolve the above problem. After the condition optimization, 3-hydroxyl-C15-phosphonate **2** can be obtained as a pale yellow solid in 93% yield.

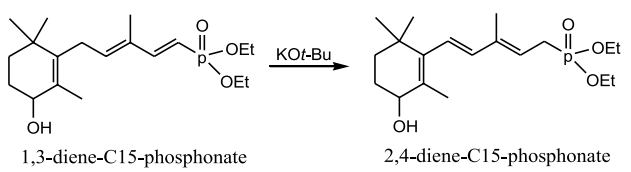
Then, 4,4′-dihydroxyl-β-carotene **8** was obtained in 68% yield by condensation of 3-hydroxyl-C15-phosphonate **2** and C10-trienedial **3** in the presence of potassium *tert*-butoxide. However, to obtain the structure of canthaxanthin, the required conversion of 1,3-diene-3-hydroxyl-C15-phosphonate to the corresponding 2,4-diene-3-hydroxyl-C15-phosphonate prior to condensation with C10-trienedial occurred in situ under these conditions (Scheme 4).

All that now remained to complete our strategy for canthaxanthin was to carry out an Oppennauer reaction of the 4,4′-dihydroxyl-β-carotene **8** catalyzed by aluminum isopropoxide. The oxidation proceeded almost quantitatively. The resulted crude canthaxanthin **1** was composed of 15–20% *cis*-isomer according to HPLC. Accordingly, an isomerization of the crude product was carried out by refluxing in isobutanol for 10 h, and then, the aubergine all-*E*-canthaxanthin was obtained in 88% yield with 97% content (GC).

Experimental

Materials and method

^{1}H NMR spectra were determined on a Bruker AVANCE DMX III 400M 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. GC analysis was carried out on a Shanghai Tianmei 7890F instrument



1,3-diene-C15-phosphonate 2,4-diene-C15-phosphonate

Scheme 4 Isomerization of 1,3-diene -C15-phosphonate to 2,4-diene-C15-phosphonate

Preparation of (*E*)-4-(1,3,3-trimethyl-7-oxa-bicyclo[4.1.0]heptan-2-yl)but-3-en-2-one 5

MCPBA (22.8 g, 0.116 mol) dissolved in CH_2Cl_2 (60 mL) was added dropwise over 30 min to a solution of α-ionone (22.2 g, 0.116 mol) in CH_2Cl_2 (85 mL) at 0 °C. The mixture was stirred for 1 h at 10 °C to complete the reaction according to TLC and GC. Then, the reaction mixture was filtered and the residue was washed with CH_2Cl_2 (50 mL). The above combined CH_2Cl_2 was then washed with 10% aq Na_2SO_3, 5% aq NaOH and water successively and dried ($MgSO_4$). The crude product epoxide **5** was afforded by concentration in vacuo in 95% yield (21.1 g) with a content of 92.6% (GC). GC–MS: *m*/*z* (%) = 208, 193, 109.

Preparation of (*E*)-4-(3-hydroxy-2,6,6-trimethylcyclohex-1-enyl)but-3-en-2-one 6

30% sodium methoxide was added to the above epoxide **5** (20.9 g, 0.1 mol) in 80 mL CH_3OH, and the mixture was stirred for 3 h in refluxing. Then, 0.5 mL glacial acetic acid was added at rt and the methanol was evaporated in vacuo. Twenty milliliters of H_2O was added to the above residue, which was then extracted by ethyl acetate (15 mL × 2). Succinic anhydride (11 g, 0.11 mol) was added into the above extract and refluxing for 5 h. After cooling to rt, saturated aq Na_2CO_3 (30 mL) was added for extraction and the organic layer was discarded. Then, the extract was acidified to PH 1–2 with 10% aq HCl, which was then extracted with ethyl acetate (30 mL × 2), followed by drying ($MgSO_4$) and distillation in vacuo to afford the corresponding ester. Then, 30% sodium methoxide (25 mL) was added and refluxing for 1 h. After cooling to rt, methanol was evaporated in vacuo and 25 mL water was added to the residue. Then, extraction with ethyl acetate (20 mL × 2), drying ($MgSO_4$) and evaporation in vacuo, a purified 4-hydroxyl-β-ionone **6** in 85% yield with 98% content (GC), was afforded. GC–MS: *m*/*z* (%) = 208, 109.

Preparation of (*E*)-4-(3-hydroxy-2,6,6-trimethylcyclohex-1-enyl)-2-methylbut-2-enal 7

A mixture of 4-hydroxyl-β-ionone **6** (20 g, 0.096 mol), methyl chloroacetate (10.5 g, 0.096 mol) and 50 mL toluene was cooled to − 20 °C, and 30% sodium methoxide (25 g) was added dropwise in 30 min. The reaction mixture was stirred for 3 h at − 10 °C. Then, 200 mL water was added and separated. The water layer was extracted with toluene (100 mL × 2). The combined organic layer was washed with water (50 mL), dried with $MgSO_4$ and

evaporated in vacuo to afford crude 4-hydroxyl-C14-aldehyde **7** (17.6 g) in 83% yield with content of 91% (GC). A purified product was obtained as a pale yellow liquid after a distillation under a vacuo of 8 Pa with the content of 94.2%. b.p. 105–108 °C (2 mmHg). ^{1}H NMR (400 Hz, $CDCl_3$): $\delta = 0.99$ (*s*, 3H, CH_3), 1.04 (*s*, 3H, CH_3), 1.68 (*s*, 6H, $2 \times CH_3$), 1.82 (*s*, 4H, CH_2CH_2), 2.18 (*s*, 1H, OH), 3.05–3.06 (*d*, 2H, CH_2), 3.97 (*s*, 1H, OCH), 6.33 (*s*, 1H, = CH), 9.38 (*s*, 1H, CHO) [18]. ESI–MS: 205 (M + 1-H_2O, 100).

Preparation of diethyl [(1*E*,3*E*)-3-methyl-5-(3-hydroxyl-2,6,6-trimethylcyclohex-2-en-2-yl)penta-1,3-dien-1-yl] phosphonate 2

Sodium (2.0 g) was dissolved in anhydrous alcohol (100 mL) under N_2. Then, tetraethyl methylenebisphosphonate (25.0 g, 0.087 mol) was added dropwise to the above sodium ethoxide solvent at 25 °C under N_2. A solution of 4-hydroxyl-C14-aldehyde **7** (17.5 g, 0.079 mol) in ethanol (30 mL) was added dropwise over 30 min at 25 °C, and the mixture was stirred for a further 2 h. After the reaction was completed according to GC, the pH value of the reaction mixture was adjusted to about 7 with acetic acid. Then, H_2O (100 mL) and acetyl acetate (100 mL) were added. The organic layer was separated, washed with 10% aq NaCl (100 mL), dried with anhydrous $MgSO_4$ and concentrated in vacuo to give the crude product as a pale yellow powder in 93% yield (25.6 g). M.p.: 115–117 °C. ^{1}H NMR (400 Hz, $CDCl_3$): $\delta = 0.85$ (*s*, 3H, CH_3), 1.01 (*s*, 3H, CH_3), 1.32–1.39 (6H, CH_3), 1.59–1.71 (*m*, 7H, CH_2CH_2, CH_3), 2.89–2.92 (*d*, 2H, CH_2), 3.04 (*s*, 1H, OCH), 4.04–4.13 (*m*, 4H, $OCH_2 \times 2$), 5.51–5.60 (*t*, 1H, = CH), 5.66–5.69 (*t*, 1H, = CH), 7.04–7.27 (*m*, 1H, = CH) [18]. ESI–MS *m*/*z* (%): 713.7 (2 M + H, 100), 735.3 (2 M + Na, 85).

Preparation of 4,4′-dihydroxyl-β-carotene 8

To a solution of KO*t*-Bu (22.5 g, 0.21 mol) in 2.5:1 (v/v) anhyd THF and HMPT (210 mL), C15-phosphonate **2b** (20 g, 0.06 mol) was added dropwise at − 25 to − 15 °C over 30 min under N_2, and the resulting mixture was stirred for further 5 h. Then, C10-trienedial **3** (4 g, 0.025 mol) in THF (50 mL) was added dropwise over 20 min. The mixture was stirred for 15 min at − 25 to − 15 °C and then stirred for further 2 h at 20 to 25 °C. Then, H_2O (500 mL) was added and THF was evaporated in vacuo. The residue was extracted with CH_2Cl_2 (2×100 mL). The organic layer was separated, washed with aqueous NaCl (5%, 3×80 mL), dried ($MgSO_4$) and evaporated to leave crude product as a purple solid in 68% yield (9.7 g).

Preparation of canthaxanthin 1

Aluminum isopropoxide (5 g, 0.0245 mol) was added to the solution of 4,4′-dihydroxyl-β-carotene (10.5 g, 0.0185 mol) and acetone (100 mL), and the mixture was stirred for 5 h at reflux temperature under N_2. Then, the solvent acetone was evaporated and 10% aq H_2SO_4 was added, followed by extracting with CH_2Cl_2 (120 mL), washing with aqueous NaCl (5%, 3×10 mL), dried ($MgSO_4$) and evaporated to leave crude canthaxanthin, in which 50 mL isobutanol was added and stirred at 80 °C for 10 h under N_2 for isomerization to afford all-*E*-canthaxanthin in 88% yield with the content of 97% (HPLC). ^{1}H NMR (400 Hz, $CDCl_3$): $\delta = 1.19$ (*s*, 12H, $4 \times CH_3$), .84 (*d*, 4H, $2 \times CH_2$), 1.87 (*s*, 6H, $2 \times CH_3$), 1.99 (*d*, 12H, $4 \times CH_3$), 2.51 (*t*, 4H, $2 \times CH_2$–C = O), 6.22–6.67 (*m*, 14H, = CH). ^{13}C NMR (100 Hz, $CDCl_3$): $\delta = 12.7$, 13.4, 27.6, 34.2, 35.6, 37.2, 124.0-141.3, 161.2, 199.3 [19, 20]. ESI–MS: 565.3 (M + 1).

Conclusions

In summary, a new route has been developed for the total synthesis of canthaxanthin with an overall yield of 37% from α-ionone. 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 canthaxanthin.

Acknowledgements This study was supported by the Public Projects of Zhejiang Province of China (No. LGG19B020002).

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