A Convenient and Stereoselective Synthesis of 11Z-3,4-Didehydroretinal by Horner–Emmons Reaction Using Diphenyl Phosphonate1)

Akimori WADA,* Fei WANG, and Masayoshi ITO
Department of Organic Chemistry for Life Science, Kobe Pharmaceutical University; 4–19–1 Motoyamakita-machi, Higashinada-ku, Kobe 658–8558, Japan.
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A convenient synthesis of 3,4-didehydroretinal was developed. The Horner–Emmons reaction between 3,4-didehydro-β-ionone and diphenyl phosphonate in the presence of crown ether gave the retinonitrile as an isomeric mixture, in which the newly produced double bond was predominantly 11Z-form. After separation of the 11Z-form retinonitrile, it was converted into the corresponding retinal in good yield without isomerization of the double bonds.

Key words visual pigment; 11Z-3,4-didehydroretinal; diphenyl phosphonate; Horner–Emmons reaction; Z-selectivity

In the visual pigment rhodopsin, the chromophore 11Z-retinal (1, vitamin A1 aldehyde) binds to the ε-amino group of a lysine residue of the apoprotein opsin through a prototinated Schiff base.3) Rhodopsin is the G-protein-coupled photoreceptor in the retina of vertebrates that initiates the visual signal transduction cascade in dim light.3) It is a representative G-protein-coupled receptors (GPCRs), and is a member of the superfamily of the seven transmembrane helix proteins, a biologically very significant class of signal mediators.4,5) Some pigments, especially those of fresh water animals, contain 11Z-3,4-didehydroretinal (2, vitamin A2 aldehyde) as well as 11Z-retinal (1) as the chromophore.5,7) For study of the mechanism of the visual process, a supply of a sufficient amount of the chromophore in pure 11Z-form is essential for the preparation of the pigment. Only one report for the stereoselective synthesis of 11Z-3,4-didehydroretinal (2) using hydrogenation of the acetylenic precursor by Lindlar catalyst has appeared in the literature.8) In the past decade, methods dealing with a stereoselective synthesis of 11Z-retinal have been developed.9—11) In connection with our stereoselective synthesis of retinoid compounds,12—15) we describe herein a convenient and stereoselective synthesis of 11Z-3,4-didehydroretinal (2) (Chart 1).

Results and Discussion
Previously, we reported a highly stereoselective synthesis of 11Z-retinal (1) from the β-ionone-tricarbonyliron-complex (3) by controlling the stereoochemistry of the newly produced double bond via the nitrile (4).13) Our first approach for the preparation of 11Z-3,4-didehydroretinal (2) was an application of this methodology. However, all our attempts were unsuccessful. Treatment of 3,4-didehydro-β-ionone (7) with dodecacarbonyltriiron in benzene afforded a complex mixture, and the desired tricarbonyliron-complex (8) was not obtained in good yield. The attempted conversion of the silyl oxytricarbonyliron-complex (5), derived from 3-silyloxy-β-ionone,17) into the 3,4-didehydro-β-ionone-tricarbonyliron-complex (8) was not achieved. Furthermore, our trials of transformation of the tricarbonyliron-complex (6), prepared according to our reported procedure,13) into the 3,4-didehydroretinal (2), including the introduction of double bond at the 3 position, was not successful under the various reaction conditions (Chart 2).

In the literature, two Horner–Emmons condensations, resulting in the formation of a new double bond predominantly

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* To whom correspondence should be addressed. e-mail: a-wada@kobepharma-u.ac.jp
in the Z configuration, have been reported.\(^{18,19}\) One method used a phosphonate with two trifluoroethyl ester groups instead of triethyl ester groups. The second method employed a diphenyl phosphonate having two bulky substituents instead of ethyl groups. In the former method, the preparation of the reagent is difficult. The latter procedure was adopted for the preparation of 11Z-retinal (I) and its analogs, and afforded the good results.\(^{20}\) Therefore, we focused our attention on the application of the latter method for the preparation of 11Z-3,4-didehydroretinal (2).

3,4-Didehydro-β-ionone (7) was treated with diisopropylcyanomethylphosphonate using sodium hydride (NaH) as a base, and gave nitrile 9 as the main product in 71% yield. The nitrile 9 was converted into the corresponding aldehyde 10 by dibutylaluminum hydride (DIBAL-H) reduction in 88% yield.

4-(Diphenylphosphono)-3-methyl-2-butenenitrile (11), prepared by the reported method (a mixture of E and Z isomers, Z/E 1:1),\(^{20}\) was treated at 0 °C with slightly less than one (95%) molar equivalent of NaH for 1 h. The resulting anion of 11 was then reacted with the aldehyde 10 affording the nitrile as an isomeric mixture, in which main product was all-E-retinonitrile (13). The stereochemistry of 13 was confirmed after DIBAL-H reduction gave the all-E-aldehyde 14.

Next, the classical reaction conditions of potassium bis(trimethylsilyl)amide (KN(TMS))/18-crown-6 at low temperature were applied for the preparation of the Z double bond.\(^{33}\) The diphenyl phosphonate (11) was treated with KN(TMS)/18-crown-6 in tetrahydrofuran (THF) at −78 °C for 1 h and the aldehyde (10) was then added to afford the nitrile (12) in 58% yield accompanied with all-E-isomer (29%). Isolated 12 was subsequently reduced with Dibal-H to give pure 11Z-3,4-didehydroretinal (2) in 75% yield. The final product was fully characterized using 1H- and 13C-NMR, and two dimensional NMR analyses (COSY, NOESY, HMBC and HMQC spectroscopy).

In summary, we have developed a convenient and stereoselective synthesis of 11Z-3,4-didehydroretinal by the Horner–Emmons reaction using diphenyl phosphonate via the nitrile intermediate. This methodology requires the separation of the isomeric mixture of retinonitrile, but it is a short, straightforward process to obtain the 11Z-form, an essential substrate for vision research.

**Experimental**

**General** IR spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrometer. 1H- and 13C-NMR spectra were obtained on Gemini-300 NMR spectrometer in CDCl3, or CD2D. Mass spectra were determined on a Hitachi M-4100 instrument. Column chromatography was performed using Merck silica gel 60. Commercially available chemicals were used without further purification except when otherwise noted. Standard workups indicates that the organic layers were finally washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo below 30 °C using a rotary evaporator. The 11-Z compounds were handled strictly in the darkroom under dim red lights. Ether refers to diethyl ether, and hexane to n-hexane.

**Tricarbonyl[(η⁴-1,2,3,4)-(3E)-4-(4-[(1,1-dimethylthylidimethylsilyloxy)-1,2,5-trimethyl-cyclohexen-1-yl)-3-buten-2-one]iron(0) (5)** A mixture of dodecaneboryliron (2.25 g, 6.9 mmol) and silyloxy-β-ionone (7.1 g, 13.9 mmol)\(^{17}\) in benzene (70 ml) was heated under reflux for 5 h. After cooling, the resulting mixture was passed through a short alumina column to remove the excess reagent. The eluent was concentrated under reduced pressure and the residue was separated by column chromatography on silica gel (eluant: hexane/ethyl acetate, 95:5, 85:15, 75:25). The mixture was then evaporated to yield a pale yellow solid (1.40 g, 60%) which was then recrystallized from hexane/ethyl acetate (85:15) to give pure 5 (80 mg, 5%).

**Tricarbonyl[(η⁶-6,7,8,9)(2E,4Z,6E,8E)-3,7-dimethyl-9-(4,4-(1,1-dimethylthylidimethylsilyloxy)-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenetrifluoroborate](iron(0)) (6)** This compound was prepared from 5 according to the previously reported method.\(^{31}\) The spectral data were as follows: IR (CHCl3) cm\(^{-1}\): 2979, 2211, 2038, 1759, 1599. 1H-NMR (CDCl3) δ: 0.05 (6H, s, Me₂), 0.88 (9H, s, Me₃), 1.18 (3H, s, Me), 1.28 (3H, s, Me), 1.42–1.61 (2H, m, CH₂), 1.80 (3H, s, Me), 1.96–2.29 (2H, m, CH₂, CH=CH₂), 2.27 (3H, s, Me), 2.34 (3H, s, Me), 3.38–3.84 (1H, m, OCH₃), 5.31 (1H, s, =CH-CN), 5.67 (1H, d, J = 11.1 Hz, =CH), 5.86–5.90 (2H, m, CH=CH₂), 6.87 (2H, m, =CH=CH₂), 7.07 (1H, d, J = 16.3 Hz, =CH), 7.23 (1H, d, J = 16.3 Hz, =CH). 13C-NMR (CDCl₃) δ: −4.69, 19.49, 21.14, 22.66, 25.83, 29.08, 30.43, 37.58, 44.70, 51.30, 55.48, 61.47, 64.77, 85.35, 96.82, 98.43, 117.50, 127.01, 131.21, 134.35, 135.18, 157.54, 211.95.

**Tricarbonyl[(η⁶-6,7,8,9)(2E,4Z,6E,8E)-3,7-dimethyl-9-(4,4-(1,1-dimethylthylidimethylsilyloxy)-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenitrile](iron(0)) (7)** To a stirred suspension of NaH (60% oil dispersion, 315 mg, 12.9 mmol) in anhydrous THF (5 ml), the reaction mixture was allowed to reach room temperature, and then cooled to 0 °C. A solution of 11Z-retinal (11) (240 mg, 71%) in THF (5 ml) was added a solution of diisopropylcyanomethylphosphonate (1.61 g, 7.88 mmol) in THF (10 ml) was added a solution of diisopropylaluminum hydride (DIBAL-H) (1.0 M in hexane, 1.14 mmol) at 0 °C, and the resulting mixture was stirred for an additional 30 min. To this solution was added a solution of diphenyl phosphonate (1.52 g, 7.88 mmol) in THF (5 ml) at 0 °C, and the resulting mixture was stirred for an additional 30 min. To this solution was added a solution of 3,4-didehydroretinal by the Horner–Emmons reaction using diphenyl phosphonate via the nitrile intermediate. This methodology requires the separation of the isomeric mixture of retinonitrile, but it is a short, straightforward process to obtain the 11Z-form, an essential substrate for vision research.

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solution was added a solution of the aldehyde 10 (90 mg, 0.40 mmol) in THF (5 ml), the reaction mixture was stirred for an additional 2 h. The reaction was quenched with saturated aqueous ammonium chloride, and then extracted with ether, followed by standard workup. The residue was purified by column chromatography on silica gel (ether:hexane = 1:4) to afford the nitrile 13 (65 mg, 56%). The spectral data of this compound were identical with those of the literature. A solution of the nitrile 13 (23 mg, 0.082 mmol) in dry hexane (5 ml) was added DIBAL-H (1 M solution in hexane, 0.12 ml, 0.12 mmol) in THF (3 ml) was added dropwise KN(TMS)₂ (0.5 M solution in toluene, 0.5 ml, 0.25 mmol) at 78 °C. The resulting mixture was stirred 1.5 h. Subsequently, homogenous silica gel (1 g, water:silica = 1:5) was added and stirring was continued for 30 min. The solids were filter through Celite and washed with diethyl ether. The filtrate was dried over Na₂SO₄. The organic solvent was evaporated and the residue was purified by flash chromatography on silica gel (ether:hexane = 1:30) to afford 14 (23 mg, 56%) in 75% yield (16 mg) as pale yellow oil. UV λ max (EtOH) nm: 254, 392. IR (CHCl₃) cm⁻¹: 3013, 2961, 2862, 1555, 1604. ¹H-NMR (CDCl₃): 1.02 (6H, s, Me×2), 1.66 (3H, s, Me), 1.73 (3H, s, Me), 1.77 (3H, s, Me), 1.98 (2H, d, J = 4.5 Hz, CH₂), 4.72 (1H, s, CH–CN), 7.53 (1H, d, J = 11.7 Hz, CH), 5.64 (1H, dt, J = 9.5, 4.5 Hz, CH), 5.82 (1H, d, J = 9.5 Hz, =CH), 6.22 (1H, dd, J = 12.5, 11 Hz, =CH), 6.23 (2H, s, =CH₂), 6.45 (1H, d, J = 12.5 Hz). ¹³C-NMR (CDCl₃): 11.79, 20.3, 20.64, 26.54, 33.86, 39.72, 99.19, 117.21, 125.34, 125.90, 128.19, 129.80, 130.09, 137.07, 138.18, 140.70, 156.46. HR-MS m/z: 279.1983 (C₁₃H₁₁O₂N) [M+H⁺].

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References and Notes