A Convenient and Stereoselective Synthesis of 11*Z*-3,4-Didehydroretinal by Horner–Emmons Reaction Using Diphenyl Phosphonate[1)]

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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 11*Z*-form. After separation of the 11*Z*-form retinonitrile, it was converted into the corresponding retinal in good yield without isomerization of the double bonds.

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

In the visual pigment rhodopsin, the chromophore 11*Z*-retinal (**1**, vitamin A_1 aldehyde) binds to the ε-amino group of a lysine residue of the apoprotein opsin through a protonated Schiff base.[2)] 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 11*Z*-3,4-didehydroretinal (**2**, vitamin A_2 aldehyde) as well as 11*Z*-retinal (**1**) as the chromophore.[6,7)] For study of the mechanism of the visual process, a supply of a sufficient amount of the chromophore in pure 11*Z*-form is essential for the preparation of the pigment. Only one report for the stereoselective synthesis of 11*Z*-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 11*Z*-retinal have been developed.[9—11)] In connection with our stereoselective synthesis of retinoid compounds,[1,12—15)] we describe herein a convenient and stereoselective synthesis of 11*Z*-3,4-didehydroretinal (**2**) (Chart 1).

Results and Discussion

Previously, we reported a highly stereoselective synthesis of 11*Z*-retinal (**1**) from the β-ionone-tricarbonyliron-complex (**3**) by controlling the stereochemistry of the newly produced double bond *via* the nitrile (**4**).[13)] Our first approach for the preparation of 11*Z*-3,4-didehydroretinal (**2**) was an application of this methodology. However, all our attempts were unsuccessful. Treatment of 3,4-didehydro-β-ionone (**7**)[16)] 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 silyloxytricarbonyliron-complex (**5**), derived from 3-silyloxy-β-ionone,[17)] into the 3,4-didehydro-β-ionone-tricarbonyliron-complex (**8**) was not achieved. Further more, 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

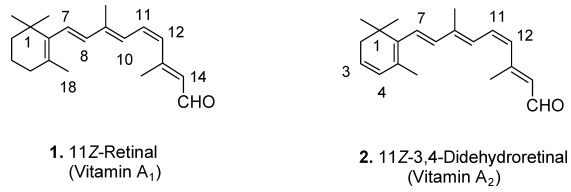

Chart 1. Structures of Vitamin A_1 and A_2

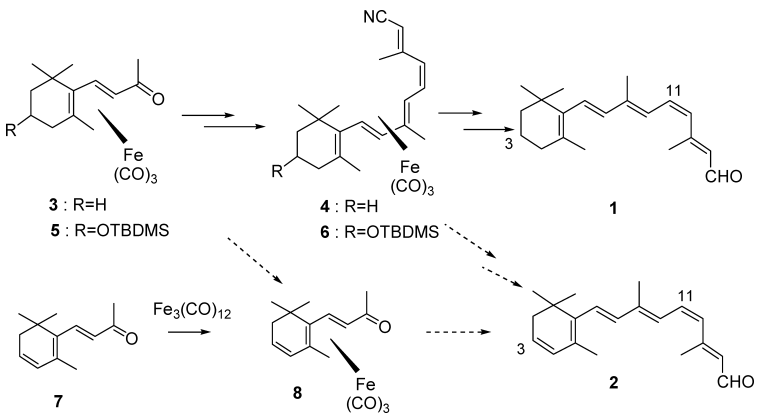

Chart 2. Synthesis of 11*Z*-3,4-Didehydroretinal Using Tricarbonyliron-Complex

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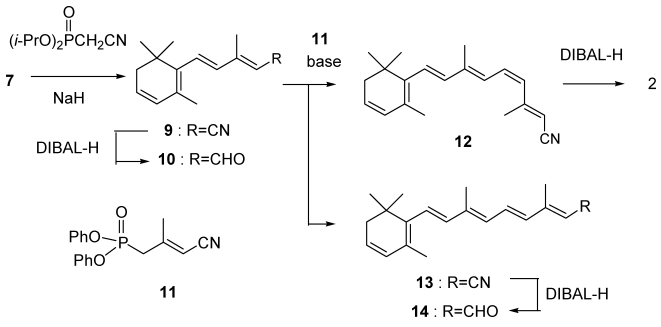

Chart 3. Synthesis of 11*Z*-3,4-Didehydroretinal by Horner–Emmons Reaction

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 11*Z*-retinal (**1**) 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 11*Z*-3,4-didehydroretinal (**2**).

3,4-Didehydro-β-ionone (**7**) was treated with diisopropyl cyanomethylphosphonate 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 diisobutylaluminum 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 : 1.1),[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)$_2$)/18-crown-6 at low temperature were applied for the preparation of the *Z* double bond.[18] The diphenyl phosphonate (**11**) was treated with KN(TMS)$_2$/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 11*Z*-3,4-didehydroretinal (**2**) in 75% yield. The final product was fully characterized using ^{1}H- and ^{13}C-NMR, and two dimensional NMR analyses (COSY, NOESY, HMBC and HMQC spectroscopy).

In summary, we have developed a convenient and stereoselective synthesis of 11*Z*-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 11*Z*-form, an essential substrate for vision research.

Experimental

General IR spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained on Gemini-300 NMR spectrometer in $CDCl_3$ or C_6D_6. 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 workup 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[(η^4-1,2,3,4)-(3*E*)-4-(4-(1,1-dimethylethyl)dimethylsilyloxy-2,6,6-trimethyl-1-cyclohexen-l-yl)-3-buten-2-one]iron(0) (5) A mixture of dodecacarbonyltriiron (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 (ether : hexane = 1 : 24) to give the iron-complex **5** in 83% yield (3.76 g). IR ($CHCl_3$) cm^{-1}: 3001, 2958, 2048, 1988, 1969, 1672. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s, Me×2), 0.87 (9H, s, Me×3), 1.33 (3H, s, Me),1.36 (3H, s, Me), 1.58—1.63 (2H, m, CH_2), 1.61 (3H, s, Me), 1.95—2.23 (2H, m, CH_2), 2.15 (3H, s, Me), 2.43 (1H, d, *J* = 8.4 Hz, =CH), 4.08—4.09 (1H, m, OCH), 5.70 (1H, d, *J* = 8.4 Hz, =CH). ^{13}C-NMR ($CDCl_3$) δ: −4.92, 18.03, 25.74, 25.80, 29.89, 31.12, 34.83, 36.11, 45.63, 49.97, 51.76, 66.10, 69.96, 82.16, 117.01, 204.36. MS-EI (negative) *m*/*z*: 462 (M^+), 434, 378, 241. HR-MS *m*/*z*: 462.1547 (Calcd for $C_{22}H_{34}FeO_5Si$: 462.1523).

Tricarbonyl[(η^4-6,7,8,9)-(2*E*,4*Z*,6*E*,8*E*)-3,7-dimethyl-9-(4-(1,1-dimethylethyl)dimethylsilyloxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenenitrile]iron(0) (6) This compound was prepared from **5** according to the previously reported method.[13] The spectral data were as follows; IR ($CHCl_3$) cm^{-1}: 2929, 2211, 2038, 1975, 1599. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s, Me_2), 0.88 (9H, s, Me×3), 1.18 (3H, s, Me), 1.28 (3H, s, Me), 1.42—1.61 (2H, m, CH_2), 1.80 (3H, s, Me), 1.96—2.22 (4H, m, CH_2, CH×2), 2.27 (3H, s, Me), 2.34 (3H, s, Me), 3.83—3.84 (1H, m, OCH), 5.31 (1H, s, =CH–CN), 5.67 (1H, d, *J* = 11.1 Hz, =CH), 5.86—5.90 (2H, m, CH×2). ^{13}C-NMR ($CDCl_3$) δ: −4.63, 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, 133.21, 134.35, 135.18, 157.54, 211.95.

(2*E*,4*E*)-3-Methyl-5-(2,6,6-trimethyl-1,3-cyclohexadienyl)-2,4-pentadienenitrile (9) To a stirred suspension of NaH (60% oil dispersion, 315 mg, 7.88 mmol) in THF (10 ml) was added a solution of diisopropyl cyanomethylphosphonate (1.61 g, 7.88 mmol) in THF (3 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-didehydro-β-ionone (**7**, 300 mg, 1.58 mmol) in THF (5 ml), the reaction mixture was allowed to reach room temperature, and then was stirred for 16 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 : 9) to afford the nitrile **9** (240 mg, 71%). The spectral data of this compound were identical with those of the literature.[21] ^{1}H-NMR ($CDCl_3$) δ: 1.00 (6H, s, Me×2), 1.83 (3H, s, Me), 2.06 (2H, d, *J* = 3.5 Hz, CH_2), 2.18 (3H, s, CH_3), 5.16 (1H, s, =CH), 5.7—5.8 (1H, m, =CH), 5.84 (1H, d, *J* = 9.5 Hz, =CH), 6.23 (1H, d, *J* = 16 Hz, =CH), 6.53 (1H, d, *J* = 16 Hz, =CH). ^{13}C-NMR ($CDCl_3$) δ: 16.21, 20.06, 26.46, 33.76, 39.60, 96.28, 117.83, 126.65, 129.38, 129.53, 131.69, 134.09, 136.67, 156.82.

(2*E*,4*E*)-3-Methyl-5-(2,6,6-trimethyl-1,3-cyclohexadienyl)-2,4-pentadienal (10) To a solution of the nitrile **9** (244 mg, 1.14 mmol) in anhydrous dichloromethane (5 ml) was added a solution of DIBAL-H (1.0 M in hexane, 1.26 ml, 1.26 mmol) at 0 °C and the resulting mixture was stirred for an additional 30 min. The reaction was quenched with moist silica gel (SiO_2 : H_2O 5 : 1) and the resulting mixture was stirred for an additional 1 h. After filtration through Celite, the filtrate was dried over sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel (ether : hexane = 1 : 9) to afford the aldehyde **10** (203 mg, 88%). The spectral data of this compound were identical with those of the literature.[21] ^{1}H-NMR ($CDCl_3$) δ: 1.03 (6H, s, Me×2), 1.86 (3H, s, Me), 2.08 (2H, d, *J* = 4 Hz, CH_2), 2.30 (3H, s, Me), 5.7—5.9 (1H, m, =CH), 5.87 (1H, d, *J* = 9.5 Hz, =CH), 5.94 (1H, d, *J* = 8 Hz, =CH), 6.30 (1H, d, *J* = 16 Hz, =CH), 6.71 (1H, d, *J* = 16 Hz, =CH), 10.11 (1H, d, *J* = 8 Hz, CHO). ^{13}C-NMR ($CDCl_3$) δ: 12.78, 20.25, 26.62, 33.95, 39.77, 126.83, 128.82, 129.61, 129.87, 134.13, 134.82, 137.23, 154.67, 191.13.

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-2,4,6,8-nonatetraenenitrile (13) To a stirred suspension of NaH (60% oil dispersion, 18 mg, 0.45 mmol) in THF (5 ml) was added a solution of diphenyl phosphonate (**11**) (150 mg, 0.48 mmol) in THF (3 ml) was added at 0 °C, and the resulting mixture was stirred for an additional 30 min. To this

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.[21] ^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, s, Me×2), 1.86 (3H, s, Me), 2.07 (3H, s, Me), 2.08 (2H, d, J=4.5 Hz, CH_2), 2.21 (3H, s, Me), 5.18 (1H, s, =CH), 5.7—5.8 (1H, m, =CH), 5.85 (1H, d, J=9.5 Hz, =CH), 6.14 (1H, d, J=11 Hz, =CH), 6.27 (1H, d, J=15.5 Hz, =CH), 6.29 (1H, d, J=15.5 Hz, =CH), 6.32 (1H, d, J=15.5 Hz, =CH), 6.95 (1H, dd, J=15, 11 Hz, =CH). ^{13}C-NMR ($CDCl_3$) δ: 12.81, 16.59, 20.27, 26.71, 33.94, 39.82, 96.55, 117.96, 125.54, 127.68, 128.38, 129.26, 129.79, 131.44, 132.37, 136.33, 138.13, 141.14, 156.85.

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-2,4,6,8-nonatetraenal (14) To 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) 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 Na_2SO_4. The organic solvent was evaporated and the residue was purified by flash chromatography (ether : hexane = 1 : 15) to give the all-*E*-3,4-didehydroretinal **14** (16 mg, 68%). The spectral data of this compound were identical with those of the literature.[21] ^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, s, Me×2), 1.87 (3H, s, Me), 2.03 (3H, s, Me), 2.09 (2H, d, J=4.5 Hz, CH_2), 2.32 (3H, s, Me), 5.7—5.8 (1H, m, =CH), 5.85 (1H, d, J=9.5 Hz, =CH), 5.97 (1H, d, J=8 Hz, =CH), 6.21 (1H, d, J=11 Hz, =CH), 6.32 (2H, br s, =CH×2), 6.38 (1H, d, J=15 Hz, =CH), 7.16 (1H, dd, J=15, 11 Hz, =CH), 10.10 (1H, d, J=8 Hz, CHO). ^{13}C-NMR ($CDCl_3$) δ: 12.85, 13.06, 20.29, 26.71, 33.95, 39.03, 125.55, 127.75, 128.44, 129.03, 129.82, 129.86, 132.38, 134.71, 136.41, 138.15, 141.07, 154.67, 191.05.

(2*E*,4*Z*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-2,4,6,8-nonatetraenenitrile (12) To a stirred solution of diphenyl phosphonate (**11**) (46 mg, 0.15 mmol) and 18-crown-6 (37 mg, 0.14 mmol) in THF (3 ml) was added dropwise $KN(TMS)_2$ (0.5 M solution in toluene, 0.28 ml, 0.14 mmol) at −78 °C, and the mixture was stirred for 1 h at −78 °C. To this solution was added a solution of the aldehyde **10** (30 mg, 0.148 mmol) in THF (4 ml). After stirring for 2 h at −78 °C, the resulting mixture was quenched with water (5 ml) and then extracted with ether, followed by standard workup. The residue was purified by column chromatography on silica gel (ether : hexane = 1 : 25) to give the nitrile **12** (23 mg, 58%) and all-*E*-isomer **13** (12 mg, 29%). The latter is identical with the sample obtained before.

11*Z*-isomer **12**: UV λ_{max} (hexane) nm: 351. IR ($CHCl_3$) cm^{-1}: 3012, 2959, 2924, 2208, 1578. ^{1}H-NMR (C_6D_6): 1.02 (6H, br, 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, CH_2), 4.72 (1H, s, =CH–CN), 5.33 (1H, d, J=11 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, =CH×2), 6.45 (1H, d, J=12.5 Hz). ^{13}C-NMR (C_6D_6): 11.79, 20.03, 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 (Calcd for $C_{20}H_{25}N$: 279.1985).

(2*E*,4*Z*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1,3-cyclohexdien-1-yl)-2,4,6,8-nonatetraenal (2) This was prepared from the nitrile **12** (21 mg, 0.0752 mmol) and DIBAL-H (1 M solution in hexane, 0.12 ml, 0.12 mmol) in the same manner as described for the preparation of **14** in 75% yield (16 mg) as pale yellow oil. UV λ_{max} (EtOH) nm: 254, 392. IR ($CHCl_3$) cm^{-1}: 3013, 2961, 2862, 1955, 1604. ^{1}H-NMR (C_6D_6): 1.02 (6H, s, Me×2), 1.68 (3H, br, Me), 1.71 (3H, br, Me), 1.76 (3H, s, Me), 1.98 (2H, dd, J=4.5, 2 Hz, CH_2), 5.55 (1H, d, J=12 Hz, =CH), 5.62—5.65 (1H, m, =CH), 5.80 (1H, dt, J=9.5, 2 Hz, =CH), 6.06 (1H, d, J=8 Hz, =CH–CO), 6.28 (2H, br, =CH), 6.33 (1H, t, J=12 Hz, =CH), 6.55 (1H, d, J=12 Hz, =CH), 9.87 (1H, d, J=8 Hz, CHO). ^{13}C-NMR (C_6D_6): 12.13, 14.36, 20.31, 26.85, 31.91, 40.03, 125.56, 126.93, 130.17, 130.54, 130.63, 131.26, 138.51, 140.71, 153.97, 189.73. HR-MS *m/z*: 282.1998 (Calcd for $C_{20}H_{26}O$: 282.1982).

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