Akimori Wada*, Naoko Fujioka and Masayoshi Ito

Kobe Pharmaceutical University, 4-19-1, Motoyamakita-machi, Higashinada-ku, Kobe 658-8558, Japan
Received May 24, 2000

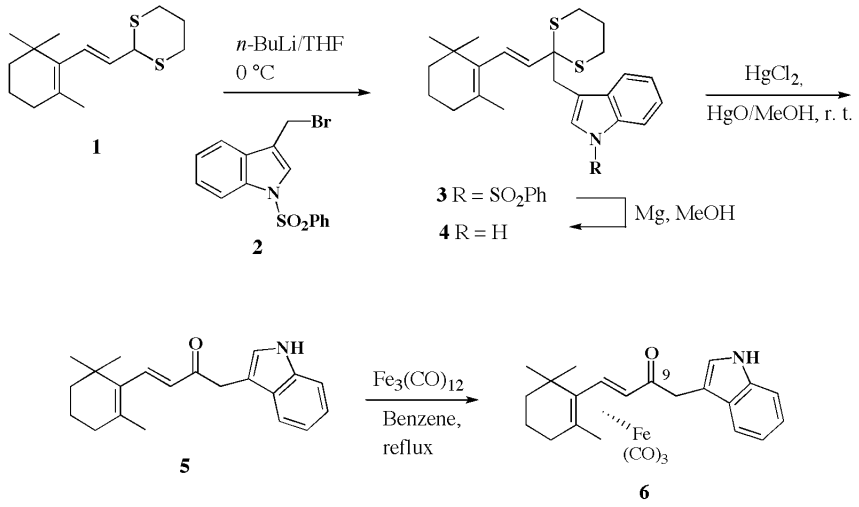
A convenient synthesis of 11*Z*-9-demethyl-9-((3-indolyl)methyl)retinal, which has an amino acid residue of tryptophan at the 9 position in retinal, is described using a tricarbonyliron complex.

J. Heterocyclic Chem., **38**, 259 (2001).

11*Z*-Retinal analogs are very important compounds for investigating the interaction between the signal molecule and apo-protein opsin in the visual transduction process of photosensitive pigments such as rhodopsin and iodopsin [2]. Recently, we reported a novel method for a stereoselective synthesis of 11*Z*-retinal from the β-ionone-tricarbonyliron complex *via* the Peterson reaction, in which the *Z*-olefin was predominantly produced [3]. Continuing our investigation for the conformational analysis of the retinal chromophore in rhodopsin [4], we attempted to prepare the 11*Z*-9-demethyl-9-((3-indolyl)methyl)retinal, which has the amino acid residue of tryptophan at the 9 position in 11*Z*-retinal, by application of our developed methodology for the synthesis of 11*Z*-retinal.

β-Ionone analog-tricarbonyliron complex **6**, in which the indole substituent was introduced on the methyl group at the 9 position, was prepared from *S,S*-acetal **1** [5] by a small modification of the previously reported method [6]. Alkylation of the lithium salt of **1**, produced by deprotonation using *n*-butyl lithium as a base, with 1-benzenesulfonyl-3-bromomethylindole **2** [7] proceeded smoothly to afford the sulfone **3** in quantitative yield. Cleavage of the *N*-benzenesulfonyl group of **3** was accomplished by magnesium metal in methanol [8] to give the acetal **4** in 88 % yield. After deprotection of the *S,S*-acetal of **4** by the usual method using mercury(II) chloride and mercury(II) oxide in methanol, the β-ionone analog **5** was converted to the corresponding tricarbonyliron complex **6** by treatment with dodecacarbonyl-triiron(0) [9] in benzene in good yield (62%). The ^{1}H-nmr, ir and high resolution mass spectral data were consistent with the indicated structure of **6** (Scheme 1).

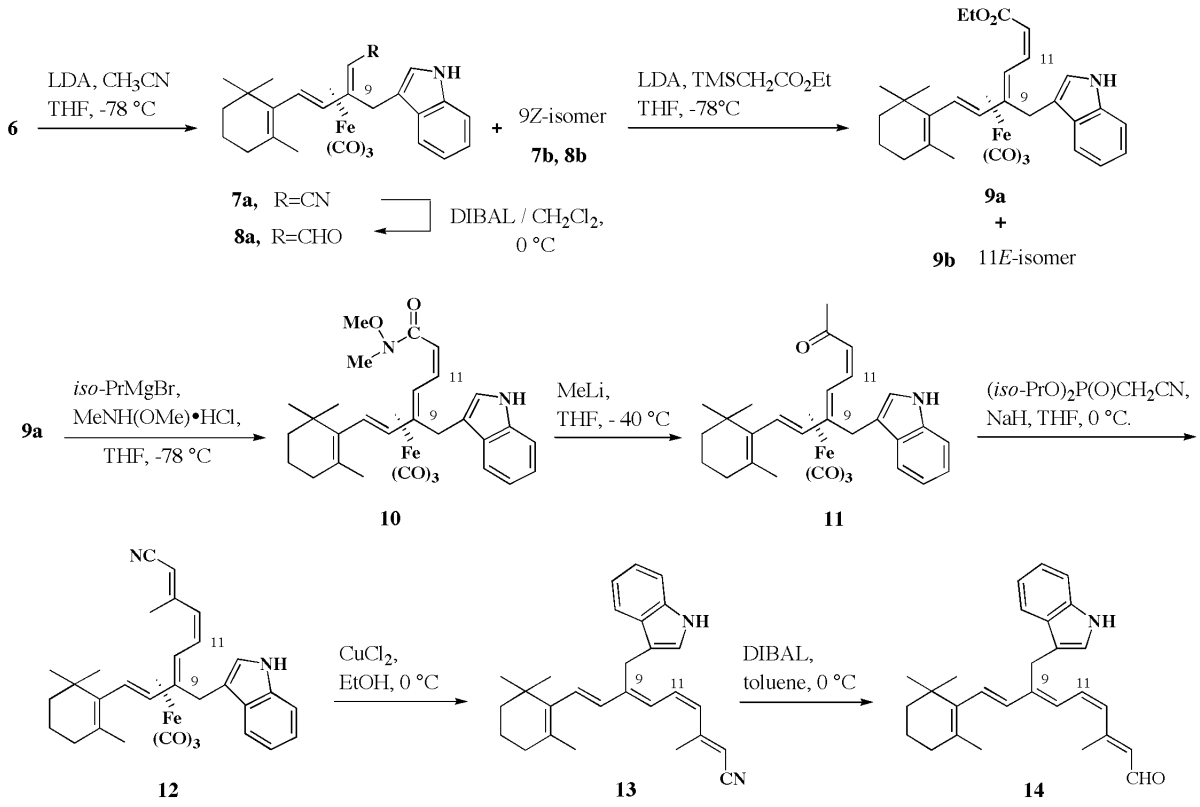
Scheme 1



Treatment of **6** with the lithium salt of acetonitrile in THF at -70 °C gave the nitrile-tricarbonyliron complexes **7a** and **7b** (ratio *ca.* 1:1) *via* addition, dehydration and subsequent migration of the tricarbonyliron complex. A similar migration of tricarbonyliron has already been reported by Salzer *et al*. in the reaction of sorbaldehyde-tricarbonyliron with carbanions[10]. These products were used in the next reaction without isolation because it is difficult to the separate them at this stage. Reduction of **7a,b** by diisobutylaluminum hydride (DIBAL-H) in dichloromethane at 0 °C afforded the aldehydes **8a** and **8b** in 49% and 31% yields, respectively. The stereochemistry at position 9 of these compounds [11] was determined by ^{1}H-NMR spectral analysis based on the fact that the chemical shift of 7-H *cis* to an aldehyde group appears further downfield due to the anisotropic effect of a

carbonyl group (δ 3.17 for **8b**, δ 2.49 for **8a)**. In contrast to our previous report for the reaction of β-ionone-tricarbonyliron complex with the lithium salt of acetonitrile [12], the stereoselective formation of *E*-isomer was lost, and almost the same amount of *E*- and *Z*-isomers were produced. We speculated that this is due to the steric bulkiness of the indole substituent, which reduces the relative thermodynamic energy difference between the isomeric products **7a** and **7b**. The Peterson reaction of **8a** using ethyl trimethylsilylacetate afforded predominantly the *Z*-ester **9a** (64%) accompanied by the *E*-ester **9b** (17%). The stereochemistry of the newly produced double bond in **9a,b** was determined based on the coupling constants of the 11-H signal in their NMR spectrum (δ 6.58, t, 11.5 Hz for **9a**, δ 7.31, dd, 15, 11 Hz for **9b**), respectively. Our first attempt at transformation of the *Z*-ester **9a** to the ketone-tricarbonyliron complex **11** directly using triphenylstannylmethyl lithium [13] was unsuccessful. So, we investigated another route for the conversion of ester **9a** was transformed to the amide **10** by the reaction with *N*-methoxy-*N*-methylamine hydrochloride in the presence of isopropylmagnesium bromide [16], quantitatively. The reaction of **10** with methyllithium proceeded smoothly to give ketone **11** in excellent yield. Among these conversions, the geometry of the 11-12 double bond was unchanged, and it was found that this method would provide a convenient alternative for the conversion of the ester to the ketone in the retinal synthesis. The Emmons-Horner reaction of ketone **11** with diisopropylcyanomethylphosphonate using sodium hydride as a base in THF gave the nitrile-tricarbonyliron complex **12** as the sole product (98% yield). The newly produced double bond was determined as *E* by comparison of ^{1}H- and ^{13}C-NMR spectral data with those of the 9-methyl analog of the tricarbonyliron complex [1]. The final transformation of nitrile **12** to the 11*Z*-retinal analog **14** was accomplished by the sequence of decomplexation with copper(II) chloride and DIBAL-H reduction (Scheme 2).

Scheme 2



into ketone **11**. It is well known that *N*-methoxy-*N*-methylamide (Weinreb amide) is a powerful tool for the conversion of acid or ester functional groups to ketones [14] and has been used for the synthesis of some natural products [15]. In order to apply this method, the ester **9a**

In summary, we have shown the preparation of the 11*Z*-9-demethyl-9-((3-indolyl)methyl)retinal by a slight modification of our previously developed method using tricarbonyliron complex. The interaction of this compound with the apoprotein of rhodopsin is under investigation.

EXPERIMENTAL

Measurements.

All melting points were determined using a Yanagimoto micro melting point apparatus and uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer. Proton and carbon magnetic resonance spectra were determined using Varian 200, 300 and 500 MHz instruments with tetramethylsilane as the internal standard. Mass spectra were obtained on a Hitachi M-80 instrument. High-performance liquid chromatography (HPLC) was performed on a Shimadzu LC-10A instrument using Chemcosorb 7-ODS-H (10 x 300 mm) column. All new compounds are unstable oils, therefore high resolution mass measurements were used to obtain molecular formula information. Due to instability their purity could not be measured by elemental analysis.

1-(Phenylsulfonyl)-3-[[2-[(*E*)-(2,6,6-trimethyl-1-cyclohexenyl)-1-ethenyl]-1,3-dithian-2-yl]-methyl]-1*H*-indole (**3**).

A solution of *n*-butyllithium (1.65 mole hexane solution, 3.1 ml, 4.93 mmoles) was added dropwise to a stirred solution of the *S*,*S*-acetal (**1**, 1.2 g, 4.48 mmoles) [4] in tetrahydrofuran (20 ml) at 0 °C. The resulting mixture was stirred for an additional 30 minutes at room temperature, and cooled to -78 °C. To the above solution, was added a solution of *N*-benzensulfonyl-3-(bromomethyl)indole (**2,** 1.25 g, 3.60 mmoles) [5] in tetrahydrofuran (4 ml) at -78 °C. After stirring for an additional 30 minutes under the same conditions, the reaction was quenched with saturated aqueous ammonium chloride (50 ml) and then extracted with ether (3 x 50 ml). The combined extracts were washed with saturated aqueous sodium chloride (80 ml) and then dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ether:hexane, 1:4) to give **3** in quantitative yield (1.96 g); ir (chloroform): 2933 cm^{-1}; uv (ethanol): 253 nm; and ^{1}H nmr (deuteriochloroform): δ 0.86 (s, 6H), 1.38–1.41 (m, 4H), 1.42 (s, 3H), 1.84–1.88 (m, 1H), 1.90–1.92 (m, 2H), 2.02–2.08 (m, 1H), 2.70–2.76 (m, 2H), 2.92–2.98 (m, 2H), 3.26 (s, 2H), 5.41 (d, 1H, *J* = 16 Hz), 6.28 (d, 1H, *J* = 16 Hz), 7.18-7.28 (m, 2H, ArH), 7.34-7.52 (m, 3H, ArH), 7. 56 (d, 1H, *J* = 8 Hz, ArH), 7.63 (s, 1H, ArH), 7.85 (d, 2H, *J* = 8 Hz, ArH), 7.93 (d, 1H, *J* = 8 Hz, ArH) ppm; ^{13}C nmr (deuteriochloroform): δ 19.2, 21.4, 25.1, 27.5 (2C), 28.8 (2C), 32.8, 33.9, 37.6, 39.4, 55.8, 113.4, 116.7, 120.0, 123.1, 124.5, 125.9, 126.8 (2C), 129.1 (2C), 129.3, 131.7, 132.0, 133.5, 134.6,135.0, 136.3, 138.3 ppm. Exact mass Calcd. for $C_{30}H_{35}NO_2S_3$: 537.1832. Found: 537.1829.

3-[[2-[(*E*)-(2,6,6-Trimethyl-1-cyclohexenyl)-1-ethenyl]-1,3-dithian-2-yl]methyl]-1*H*-indole (**4**).

To a solution of **3** (1 g, 1.86 mmoles) in methanol (20 ml), magnesium metal (1.5 g, 62.5 mmoles) was added all at once at 0 °C. The resulting mixture was stirred for 20 hours at room temperature, and the reaction was quenched with saturated aqueous ammonium chloride (50 ml). After removal of methanol, the residue was extracted with ether (3 x 100 ml). The combined extracts were washed with saturated aqueous sodium chloride (100 ml), and then dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ether:hexane, 1:9) to give **4** in 88% yield (0.65 g) as a colorless oil; ir (chloroform): 3480, 2932, 2361 cm^{-1}; uv (ethanol): 390, 383, 222 nm; ^{1}H nmr (deuteriochloroform): δ 0.93 (s, 6H), 1.41–1.58 (m, 4H), 1.59 (s, 3H), 1.84–1.89 (m, 1H), 1.96 (brt, 2H, *J* = 6 Hz), 2.02–2.08 (m, 1H), 2.67–2.72 (m, 2H), 2.93–2.99 (m, 2H), 3.35 (s, 2H), 5.53 (d, 1H, *J* = 16 Hz), 6.32 (d, 1H, *J* = 16 Hz), 7.10 (t, 1H, *J* = 8 Hz, ArH), 7.15 (t, 1H, *J* = 8 Hz, ArH), 7.19 (s, 1H, ArH), 7.30 (d, 1H, *J* = 8 Hz, ArH), 7.70 (d, 1H, *J* = 8 Hz, ArH), 8.04 (brs, 1H, NH) ppm; ^{13}C nmr (deuteriochloroform): δ 19.2, 21.7, 25.2, 27.5 (2C), 28.9 (2C), 32.9, 34.1, 38.4, 39.5, 57.0, 109.8, 110.9, 119.3, 119.5, 121.8, 124.2, 128.6, 129.0, 131.2, 135.6, 136.0, 136.6 ppm. Exact mass Calcd. for $C_{24}H_{31}NS_2$: 397.1899. Found: 397.1901.

(3*E*)-1-(3-Indolyl)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (**5**)

To a solution of **4** (105 mg, 0.26 mmole) in methanol (80 ml), was added mercury (II) chloride (180 mg, 0.66 mmole) and mercury(II) oxide (86 mg, 0.40 mmole) and the resulting mixture was stirred for 15 minutes at room temperature. After removal of methanol, the crude product was isolated by filtration through Celite with ether and the filtration was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ether:hexane, 1:4) to give **5** in 68% yield (55.5 mg) as a red oil; ir (chloroform): 3479, 3019, 2935, 1677, 1600 cm^{-1}; uv (ethanol): 290, 220 nm; ^{1}H nmr (deuteriochloroform): δ 0.97 (s, 6H), 1.40–1.60 (m, 4H), 1.63 (s, 3H), 2.01 (t, 2H, *J* = 6.5 Hz), 3.98 (s, 2H), 6.23 (d, 1H, *J* = 16 Hz), 7.11 (s, 1H, ArH), 7.12 (td, 1H, *J* = 8, 1Hz, ArH), 7.19 (td, 1H, *J* = 8, 1Hz, ArH), 7.34 (d, 1H, *J* = 8 Hz, ArH), 7.41 (d, 1H, *J* = 16 Hz), 7.59 (d, 1H, *J* = 8 Hz, ArH), 8.09 (brs, 1H, NH) ppm; ^{13}C nmr (deuteriochloroform): δ 18.2, 21.6, 28.7 (2C), 33.6, 34.0, 38.2, 39.8, 109.2, 111.1, 118.8, 119.6, 122.1, 123.0, 127.4, 129.2, 136.1, 136.2, 136.4, 142.6, 198.3 ppm. Exact mass Calcd. for $C_{21}H_{25}NO$: 307.1937. Found: 307.1917.

Tricarbonyl[(η^4-3,4,1,2)-(3*E*)-1-(3-indolyl)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one]iron(0) (**6**).

A mixture of **5** (232 mg, 0.76 mmole) and dodecacarbonyltriiron (570 mg, 1.13 mmoles) in benzene (50 ml) was heated under reflux for 4 hours. After cooling, the resulting mixture was passed through a short alumina column to remove the excess reagent. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ether:hexane, 1:4) to give **6** in 62% yield (202mg) as a yellow oil; ir (chloroform): 3480, 2933, 2047, 1987, 1970, 1668 cm^{-1}; uv (ethanol): 260, 217 nm; ^{1}H nmr (deuteriochloroform): δ 0.90 (s, 3H), 1.24–1.30 (m, 2H), 1.37 (s, 3H), 1.38 (s, 3H), 1.42–1.58 (m, 2H), 1.78–1.82 (m, 2H), 2.48 (d, 1H, *J* = 9 Hz), 3.78 (d, 1H, *J* = 16 Hz), 3.83 (d, 1H, *J* = 16 Hz), 5.63 (d, 1H, *J* = 9 Hz), 7.13 (t, 1H, *J* = 8 Hz, ArH), 7.18 (s, 1H, ArH), 7.20 (t, 1H, *J* = 8 Hz, ArH), 7.37 (d, 1H, *J* = 8 Hz, ArH), 7.59 (d, 1H, *J* = 8 Hz, ArH), 8.11 (brs, 1H, NH) ppm; ^{13}C nmr (deuteriochloroform): 19.5, 23.7, 29.6, 34.0, 35.2, 38.7, 40.0, 42.3, 49.4, 69.8, 82.1, 109.8, 111.2, 116.9, 118.8, 119.8, 122.2, 123.1, 127.4, 136.3, 187.2, 205.9 (3C) ppm. Exact mass Calcd. for $C_{24}H_{25}FeNO_4$: 447.1134. Found: 447.1149.

Tricarbonyl[(η4-2,3,4,5)-(2*E*,4*E*)-3-(3-indolyl)methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal]iron(0) (**8a**) and Tricarbonyl[(η4-2,3,4,5)-(2*Z*,4*E*)-3-(3-indolyl)methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal]iron(0) (**8b**).

To a solution of LDA, prepared from *n*-butyllithium (1.65 mole hexane solution, 1.92 ml, 3.2 mmoles) and diisopropylamine (0.43 ml, 3.2 mmoles) in tetrahydrofuran (10 ml) was added a solution of acetonitrile (0.18 ml, 3.2 mmoles) at -78 °C, and the resulting mixture was stirred for an additional 20 minutes. A solution of **6** (277 mg, 0.64 mmole) in tetrahydrofuran (5 ml) was added at -78 °C, and the resulting mixture was stirred for an additional 20 minutes. The reaction was quenched with saturated aqueous ammonium chloride (20 ml), and then extracted with ether (2 x 30 ml). The combined extracts were washed with saturated aqueous sodium chloride, and then dried with sodium sulfate. The solvent was removed under reduced pressure to give the nitriles **7a** and **7b** (232 mg, 77%). To the isomeric mixture of **7** (445 mg, 1 mmole) in anhydrous dichloromethane (10 ml) was added a solution of DIBAL-H (1.0 mole hexane solution, 1.4 ml, 1.4 mmoles) in anhydrous dichloromethane (5 ml) at 0 °C, and the resulting mixture was stirred for an additional 15 minutes. After the reaction was quenched with water (20 ml), and after adding dichloromethane (80 ml), the resulting mixture was filtrated through Celite. The organic layer was separated and then dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ether:hexane, 1:4) to give the aldehydes **8a** (222 mg, 49%) and **8b** (137 mg, 31%) as an orange solid, respectively.

E-isomer **8a** had ir (chloroform): 3477, 2927, 2049, 1981, 1659 cm^{-1}; uv (ethanol): 269, 219 nm; ^{1}H nmr (deuteriochloroform): δ 0.98 (s, 3H), 1.13 (s, 3H), 1.18 (d, 1H, *J* = 6.5 Hz), 1.26-1.52 (m, 4H), 1.72 (s, 3H), 1.97-1.99 (m, 2H), 2.49 (d, 1H, *J* = 11.5 Hz), 4.17 (d, 1H, *J* = 15.5 Hz), 4.48 (d, 1H, *J* = 15.5 Hz), 5.81 (d, 1H, *J* = 11.5 Hz), 7.13 (brs, 1H, ArH), 7.17 (t, 1H, *J* = 8 Hz, ArH), 7.24 (t, 1H, *J* = 8 Hz, ArH), 7.27 (d, 1H, *J* = 8 Hz, ArH), 7.73 (d, 1H, *J* = 8 Hz, ArH), 8.12 (brs, 1H, NH), 9.62 (d, 1H, *J* = 6.5 Hz) ppm; ^{13}C nmr (deuteriochloroform): δ 18.7, 23.0, 29.4, 29.5, 31.6, 34.8, 35.2, 42.2, 55.5, 66.4, 88.6, 101.9, 111.4, 114.2, 118.7. 119.9, 122.5, 122.6, 127.1, 134.7, 136.2, 137.3, 195.3, 210.3 (3C) ppm. Exact mass Calcd. for $C_{26}H_{27}NFeO_4$: 473.1291. Found: 473.1261.

Z-Isomer **8b** had ir (chloroform): 3478, 2935, 2049, 1992, 1668 cm^{-1}; uv (ethanol): 266, 219 nm; ^{1}H nmr (deuteriochloroform): δ 0.92 (s, 3H), 1.11 (s, 3H), 1.26-1.50 (m, 4H), 1.62 (s, 3H), 1.93-1.96 (m, 2H), 3.12 (d, 1H, *J* = 3Hz), 3.17 (d, 1H, *J* = 11.5 Hz), 3.89 (d, 1H, *J* = 16 Hz), 3.98 (d, 1H, *J* = 16 Hz), 5.99 (d, 1H, *J* = 11.5 Hz), 7.13 (s, 1H, ArH), 7.18 (t, 1H, *J* = 8 Hz, ArH), 7.24 (t, 1H, *J* = 8 Hz, ArH), 7.40 (d, 1H, *J* = 8 Hz, ArH), 7.72 (d, 1H, *J* = 8 Hz, ArH), 8.13 (brs, 1H, NH), 9.32 (d, 1H, *J* = 3 Hz) ppm ; ^{13}C nmr (deuteriochloroform): δ 18.8, 23.0, 28.6, 29.6, 34.3, 34.8, 35.4, 42.1, 57.8, 68.9, 94.6, 103.4, 111.3, 114.1, 118.7, 120.0, 122.5, 122.7, 127.2, 135.4, 136.1, 137.1, 194.2, 210.1 (3C) ppm. Exact mass Calcd. for $C_{26}H_{27}NFeO_4$: 473.1291. Found: 473.1269.

Tricarbonyl[ethyl (η4-4,5,6,7)-(2*Z*,4*E*,6*E*)-5-(3-indolyl)methyl-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6-heptatrienoate]iron(0) (**9a**) and Tricarbonyl[ethyl (η4-4,5,6,7)-(2*E*,4*E*,6*E*)-5-(3-indolyl)methyl-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6-heptatrienoate]iron(0) (**9b**).

To a solution of LDA, prepared from *n*-butyllithium (1.53 mole hexane solution, 0.57 ml, 0.87 mmole) and diisopropylamine (0.12 ml, 0.87 mmole) in tetrahydrofuran (10 ml) was added a solution of ethyl (trimethylsilyl)acetate (0.16 ml, 0.87 mmoles) at -78 °C, and the resulting mixture was stirred for an additional 20 minutes. A solution of **8a** (82.6 mg, 0.17 mmoles) in tetrahydrofuran (10 ml) was added at -78 °C, and the resulting mixture was further stirred for 20 minutes. The reaction was quenched with saturated aqueous ammonium chloride (20 ml) and then extracted with ether (2 x 30 ml). The combined extracts were washed with saturated aqueous sodium chloride (50 ml), and then dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ether:hexane, 1:4) to give the esters **9a** (57.2 mg, 66%) and **9b** (14.4 mg, 13%) as a orange oil, respectively.

Z-Isomer **9a** had ir (chloroform): 3479, 2960, 2038, 1979, 1698, 1610 cm^{-1}; uv (ethanol): 281, 208 nm; ^{1}H nmr (deuteriochloroform): δ 1.00 (s, 3H), 1.13 (s, 3H), 1.28 (t, 3H, *J* = 7 Hz), 1.34–1.60 (m, 4H), 1.77(s, 3H), 1.96 (brt, 2H, *J* = 5 Hz), 2.47 (d, 1H, *J* = 11 Hz), 3.20 (d, 1H, *J* = 11.5 Hz), 3.99 (d, 1H, *J* = 16 Hz), 4.12–4.20 (m, 2H), 4.20 (d, 1H, *J* = 16 Hz), 5.65 (d, 1H, *J* = 11.5 Hz), 5.71 (d, 1H, *J* = 11 Hz), 6.58 (t, 1H, *J* = 11.5 Hz), 7.09 (brs, 1H, ArH), 7.17 (brt, 1H, *J* = 6.5 Hz, ArH), 7.23 (brt, 1H, *J* = 6.5 Hz, ArH), 7.40 (d, 1H, *J* = 8 Hz, ArH), 7.73 (d, 1H, *J* = 8 Hz, ArH), 8.07 (brs, 1H, NH) ppm; ^{13}C nmr (deuteriochloroform): δ 14.4, 18.9, 23.0, 28.7, 29.0, 29.7, 34.8, 35.1, 42.3, 53.5, 59.9, 63.8, 86.5, 100.9, 111.3, 114.5, 116.1, 118.8, 119.8, 122.4 (2C), 122.4, 127.2, 135.2, 135.5, 136.2, 145.7, 212.0 (3C) ppm. Exact mass Calcd. for $C_{30}H_{33}FeNO_5$: 543.1710. Found: 543.1692.

E-Isomer **9b** had ir (chloroform): 3479, 2932, 2039, 1978, 1699, 1623 cm^{-1}; uv (ethanol): 282, 211 nm; ^{1}H nmr (deuteriochloroform): 0.98 (s, 3H), 1.12 (s, 3H), 1.30 (t, 3H, *J* = 7Hz), 1.34–1.59 (m, 4H), 1.58 (d, 1H, *J* = 11Hz), 1.72 (s, 3H), 1.96 (brt, 2H, *J* = 4.5Hz), 2.21 (d, 1H, *J* = 11Hz), 4.01 (d, 1H, *J* = 15Hz), 4.20 (d, 1H, *J* = 15Hz), 4.20 (q, 2H, *J* = 7Hz), 5.73 (d, 1H, *J* = 11Hz), 5.98 (d, 1H, *J* = 15Hz), 7.11 (brs, 1H, ArH), 7.16 (t, 1H, *J* = 8Hz, ArH), 7.23 (t, 1H, *J* = 8Hz, ArH), 7.31 (dd, 1H, *J* = 15, 11Hz), 7.39 (d, 1H, *J* = 8Hz, ArH), 7.76 (d, 1H, *J* = 8Hz, ArH), 8.10 (brs, 1H, NH) ppm ; ^{13}C nmr (deuteriochloroform): δ 14.3, 18.8, 22.9, 28.6, 29.6, 29.7, 34.8, 35.1, 42.3, 56.3, 60.2, 63.4, 86.0, 100.9, 111.3, 114.2, 118.9, 119.2, 119.8, 122.4, 122.5, 127.2, 135.1, 135.7, 136.2, 145.9, 166.7, 211.9 (3C) ppm. Exact mass Calcd. for $C_{30}H_{33}FeNO_5$: 543.1710. Found: 543.1693.

Tricarbonyl[(η4-4,5,6,7)-(2*Z*,4*E*,6*E*)-*N*-methoxy-*N*-methyl-5-(3-indolyl)methyl-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6-heptatrienamido]iron(0) (**10**).

To a solution of the ester **9a** (22.4 mg, 0.04 mmoles) and *N*,*O*–dimethylhydroxylamine hydrochloride (48 mg , 0.5 mmole) in tetrahydrofuran (5 ml) was added dropwise isopropylmagnesium bromide (0.63 *M* solution, 11.4 ml, 1 m) at -78 °C. After stirring for an additional 30 minutes, the reaction was quenched with saturated aqueous ammonium chloride (10 ml) and then extracted with ether (2 x 20 ml). The combined extracts were washed with saturated aqueous sodium chloride (30 ml), and then dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ether:hexane, 1:4) to give the amide **10** (17.7 mg, quant.); ir (potassium bromide): 3479, 2935, 2036, 1976, 1639, 1600 cm^{-1}; uv (ethanol): 282, 206 nm; ^{1}H nmr (deuteriochloroform): δ 0.98 (s, 3H), 1.10 (s, 3H), 1.22–1.52 (m, 4H), 1.77 (s, 3H), 1.94-1.98 (m, 2H), 2.48 (d, 1H, *J* = 11 Hz), 3.20 (s, 3H), 3.47 (d, 1H,

J = 11.5 Hz), 3.67 (s, 3H), 3.98 (d, 1H, *J* = 16 Hz), 4.15 (d, 1H, *J* = 16 Hz), 5.67 (d, 1H, *J* = 11 Hz), 6.18 (d, 1H, *J* = 11.5 Hz), 6.49 (t, 1H, *J* = 11.5 Hz), 7.10 (brs, 1H, ArH), 7.17 (t, 1H, *J* = 8 Hz, ArH), 7.23 (t, 1H, *J* = 8 Hz, ArH), 7.39 (d, 1H, *J* = 8 Hz, ArH), 7.73 (d, 1H, *J* = 8 Hz, ArH), 8.07 (brs, 1H, NH) ppm; ^{13}C nmr (deuteriochloroform): δ 18.9, 23.1, 28.6, 29.0, 29.7, 32.0, 34.7, 35.0, 42.4, 54.5, 61.6, 63.8, 86.2, 100.9, 111.2, 114.4, 114.7, 118.8, 119.7, 122.3, 122.5, 127.2, 135.2, 135.3, 136.2, 144.0, 166.8, 212.4 (3C) ppm. Exact mass Calcd. for $C_{30}H_{33}FeN_2O_5$ (M-H): 557.1740. Found: 557.1752.

Tricarbonyl[(η^4-5,6,7,8)-(3*Z*,5*E*,7*E*)-6-(3-indolyl)methyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3,5,7-octatrien-2-one]iron(0) (**11**).

To a solution of the amide **10** (141 mg, 0.25 mmoles) in tetrahydrofuran (10 ml) was added dropwise methyl lithium (1.09 *M* solution, 0.93 ml, 1 mmole) at -40 °C. After stirring for an additional 10 minutes, the reaction was quenched with saturated aqueous ammonium chloride (20 ml) and then extracted with ether (2 x 30 ml). The extract was washed with saturated aqueous sodium chloride (30 ml), and then dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ether:hexane, 1:4) to give ketone **11** (127 mg, 98%) as a orange oil; ir (potassium bromide): 3479, 2934, 2038, 1980, 1673 cm^{-1}; uv (ethanol): 282, 222 nm; ^{1}H nmr (deuteriobenzene): δ 1.06 (s, 3H), 1.21 (s, 3H), 1.25–1.40 (m, 4H), 1.70–1.74 (m, 2H), 1.78 (s, 3H), 1.82 (s, 3H), 2.78 (d, 1H, *J* = 11 Hz), 3.80 (d, 1H, *J* = 16 Hz), 3.95 (d, 1H, *J* = 11 Hz), 4.06 (d, 1H, *J* = 16 Hz), 5.61 (d, 1H, *J* = 11 Hz), 5.69 (d, 1H, *J* = 11 Hz), 6.31 (t, 1H, *J* = 11 Hz), 6.63–6.64 (m, 1H, ArH), 6.75 (brs, 1H, NH), 7.03–7.05 (m, 1H, ArH), 7.21–7.24 (m, 2H, ArH), 7.70–7.72 (m, 1H, ArH) ppm; ^{13}C nmr (deuteriobenzene): δ 19.2, 23.1, 28.6, 28.8, 29.8, 31.4, 35.0, 35.2, 42.5, 55.3, 65.1, 86.6, 102.3, 111.5, 114.2, 119.1, 120.0, 122.5 (2C), 122.6, 122.9, 135.4, 136.1, 136.6, 144.2, 197.6, 212.8 (3C) ppm. Exact mass Calcd. for $C_{29}H_{31}FeNO_4$: 513.1604. Found: 513.1586.

Tricarbonyl[(η^4-6,7,8,9)-(2*E*,4*Z*,6*E*,8*E*)-7-(3-indolyl)methyl-3-methyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenenitrile]iron(0) (**12**).

To a solution of sodium hydride (60% oil dispersion, 45 mg, 1.15 mmoles) in tetrahydrofuran (5 ml) was added drowise diisopropylcyanomethylphosphonate (0.22 ml, 1.15 mmoles) at 0 °C. After stirring for an additional 30 minutes at room temperature, and to this mixture was added a solution of the ketone **11** (116 mg, 0.23 m) in tetrahydrofuran (5 ml) at 0 °C. The resulting mixture was allowed to come to the room temperature and stirred for 24 hours. The reaction was quenched with saturated aqueous ammonium chloride (10 ml) and then extracted with ether (2 x 20 ml). The combined extracts were washed with saturated aqueous sodium chloride (20 ml), and then dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ether:hexane, 1:9) to give the tricarbonyliron complex **12** (120 mg, 99%) as a orange oil; ir (potassium bromide): 3479, 2933, 2211, 2036, 1974 cm^{-1}; uv (ethanol): 320, 289, 222 nm; ^{1}H nmr (deuteriobenzene): δ 1.01 (s, 3H), 1.17 (s, 3H), 1.21–1.38 (m, 4H), 1.63 (s, 3H), 1.68–1.74 (m, 2H), 1.93 (s, 3H), 1.98 (d, 1H, *J* = 12 Hz), 2.20 (d, 1H, *J* = 11 Hz), 3.73 (d, 1H, *J* = 16 Hz), 3.97 (d, 1H, *J* = 16 Hz), 4.83 (s, 1H), 5.33 (d, 1H, *J* = 12 Hz), 5.66 (d, 1H, *J* = 11 Hz), 5.87 (t, 1H, *J* = 12 Hz), 6.61 (brs, 1H, NH), 6.69 (brs, 1H, ArH), 7.04–7.06 (m, 1H, ArH), 7.21–7.24 (m, 2H, ArH), 7.72–7.74 (m, 1H, ArH) ppm; ^{13}C nmr (deuteriobenzene): δ 19.1, 20.7, 22.9, 28.8, 29.0, 29.6, 34.9, 35.1, 42.6, 55.8, 64.3, 85.7, 99.6, 100.5, 111.7, 113.9, 117.3, 119.1, 120.1, 122.4, 122.7, 134.8, 135.3, 136.4, 136.6, 156.7, 212.9 (3C) ppm, and two carbons were hidden by benzene peak. Exact mass Calcd. for $C_{31}H_{32}FeN_2O_3$: 536.1764. Found: 536.1746.

(2*E*,4*Z*,6*E*,8*E*)-7-(3-Indolyl)methyl-3-methyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenenitrile (**13**).

To a solution of the tricarbonyliron complex **13** (120 mg, 0.22 m) in ethanol (2 ml) was added a solution of anhydrous copper(II) chloride (151 mg, 1.1 mmoles) in ethanol (3 ml) at 0 °C. After stirring for an additional 20 minutes, the reaction was quenched with saturated aqueous ammonium chloride (10 ml) and then extracted with ether (2 x 30 ml). The combined extracts were washed with saturated aqueous sodium chloride (30 ml), and then dried with sodium sulfate. The solvent was removed under reduced pressure, and then the residue was chromatographed on silica gel (ether:hexane, 1:4) to give the nitrile **13** (93 mg, quant.) as a yellow oil; ir (potassium bromide): 3413, 2927, 2864, 2208, 1572 cm^{-1}; uv (ethanol): 351, 290, 222 nm; ^{1}H nmr (deuteriobenzene): δ 0.89 (s, 6H), 1.20–1.60 (m, 4H), 1.68 (s, 3H), 1.88 (s, 3H), 1.90 (brt, 2H, *J* = 5.5 Hz), 3.83 (s, 2H), 4.77 (s, 1H), 5.33 (d, 1H, *J* = 12 Hz), 6.24 (d, 1H, *J* = 16 Hz), 6.43 (t, 1H, *J* = 12 Hz), 6.49 (d, 1H, *J* = 16 Hz), 6.53 (brs, 1H, ArH), 6.60 (d, 1H, *J* = 12 Hz), 6.61 (brs, 1H, NH), 7.03–7.04 (m, 1H, ArH), 7.22–7.24 (m, 2H, ArH), 7.69–7.71 (m, 1H, ArH) ppm ; ^{13}C nmr (deuteriobenzene): δ 19.6, 21.0, 21.9, 23.1, 28.9 (2C), 33.2, 34.5, 39.8, 99.8, 111.5, 114.2, 117.5, 118.8, 119.8, 121.9, 122.5, 125.8, 129.9, 130.7, 131.0, 136.5, 136.7, 138.1, 144.4, 156.8 ppm, and two carbons were hidden by benzene peak. Exact mass Calcd. for $C_{28}H_{32}N_2$: 396.2567. Found: 396.2579.

(2*E*,4*Z*,6*E*,8*E*)-7-(3-Indolyl)methyl-3-methyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)- 2,4,6,8-nonatetraenal (**14**).

To a solution of the nitrile **13** (93 mg 0.23 mmole) in toluene (5 ml) was added dropwise a solution of DIBAL-H (1 mole hexane solution, 0.35 ml, 0.35 m) at 0 °C. After stirring for an additional 10 minutes, the reaction was quenched with water and then extracted with ether (2 x 20 ml). The combined extracts were washed with saturated aqueous sodium chloride and then dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by reverse phase preparative HPLC (water:methanol, 1: 9) to give the aldehyde **14** (9.2 mg, 10%) as a red oil; ir (potassium bromide): 3385, 2926, 2854, 1654, 1570 cm^{-1}; uv (ethanol): 375, 286, 256, 226 nm; ^{1}H nmr (deuteriobenzene): δ 0.88 (s, 6H), 1.50–1.54 (m, 4H), 1.66 (s, 3H), 1.79 (s, 3H), 1.88 (brt, 2H, *J* = 5.5 Hz), 3.86 (s, 2H), 5.55 (d, 1H, *J* = 12 Hz), 6.16 (d, 1H, *J* = 8 Hz), 6.28 (d, 1H, *J* = 16 Hz), 6.50 (d, 1H, *J* = 16 Hz), 6.55–6.56 (m, 1H, ArH), 6.54 (t, 1H, *J* = 12 Hz), 6.63 (brs, 1H, NH), 6.81 (d, 1H, *J* = 12 Hz), 7.03–7.06 (m, 1H, ArH), 7.22–7.23 (m, 2H, ArH), 7.69–7.71 (m, 1H, ArH), 9.92 (d, 1H, *J* = 8 Hz) ppm; ^{13}C nmr (deuteriobenzene): δ 17.5, 19.6, 21.9, 23.1, 28.9 (2C), 33.2, 34.5, 39.8, 111.5, 114.2, 118.9, 119.8, 121.9 (2C), 122.4, 126.5, 129.9, 130.6, 130.8, 130.9, 131.6, 136.6, 136.7, 138.1, 144.1, 154.1, 190.0 ppm. Exact mass Calcd. for $C_{28}H_{33}NO$ 399.2564. Found: 399.2572.

Acknowledgment.

This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture (Japan) and the Science Research Promotion Fund from Japan Private School Promotion Foundation.

REFERENCES AND NOTES

[1] Retinoid and related coumpound. Part 24. For 23 see; A. Wada, N. Fujioka, Y. Tanaka and M. Ito, *J. Org. Chem.*, **65**, 2438 (2000).

[2] H. C. Saari, In The Retinoids, Biology, Chemistry, and Medicine, M. B. Sporn, A. B. Roberts, D. S. Goodman eds, Raven Press, New York, 1994, pp 351-386.

[3] A. Wada, Y. Tanaka, N. Fujioka and M. Ito, *Bioorg. Med. Chem. Lett.* **6**, 2049 (1996).

[4a] A. Wada, M. Sakai, Y. Imamoto, T. Shichida, M. Yamauchi and M. Ito, J. *Chem. Soc., Perkin I*, 1773 (1997); [b] Y. Imamoto, M. Sakai, Y. Katsuta, A. Wada, M. Ito, and Y. Shichida, *Biochemistry*, **35**, 6257 (1996).

[5] M. H. Park, T. Yamamoto and K. Nakanishi, *J. Am. Chem. Soc.*, **111**, 4997 (1989).

[6] A. Wada, N. Fujioka and M. Ito, *Chem. Pharm. Bull.*, **47**, 171 (1999).

[7] R. Liu, P. Zhang, T. Gan and J. M. Cook, *J. Org. Chem.*, **62**, 7447 (1997).

[8] H. Muratake and M. Natume, *Heterocycles*, **29**, 783 (1989).

[9] W. MacFarlane and G. Wilkinson, *Inorg. Synth.*, **8**, 181 (1966).

[10] A. Hafner, W. von Philpsborn and A. Saltzer, *Angew. Chem., Int. Ed. Engl.* **24**, 126 (1985).

[11] For structural comparisons standard retinoid numbering has been used.

[12a] A. Wada, S. Hiraishi and M. Ito, *Chem. Pharm. Bull.*, **42**, 757 (1994); [b] A. Wada, S. Hiraishi, N. Takamura, T. Date, K. Aoe and M. Ito, *J. Org. Chem.* **62**, 4343 (1997).

[13] T. Sato, H. Matsuoka, T. Igarashi, M. Minomura and E. Murayama. *J. Org. Chem*., **53**, 1207 (1988).

[14] S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, **22**, 3815 (1981).

[15a] S. Hanessian, J. –M. Fu, J. L. Chara and R. D. Fabio, *Tetrahedron Lett.*, **34**, 4157 (1993); [b] A. D. Evans, S. W. Kaldor, T. K. Jones, J. Clardy and T. J. Stout, *J. Am. Chem. Soc.*, **112**, 7001 (1990).

[16] J. M. Williams, R. B. Jobson, N. Yasuda, G. Marchesini, U.-H. Dolling and E. J. J. Grabowski, *Tetrahedron Lett.*, **36**, 5461 (1995).