A Highly Stereoselective Synthesis of 11*Z*-Retinal Using Tricarbonyliron Complex†

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A stereoselective synthesis of 11*Z*-retinal **2**, which is the chromophore of visual pigment (rhodopsin), was accomplished from the *β*-ionylideneacetaldehyde−tricarbonyliron complex **3**. The Peterson reaction of **3** using ethyl trimethylsilylacetate smoothly proceeded to afford predominantly the *Z*-ester **6**. Transformation of the *Z*-ester **6** to the methyl ketone **19**, followed by the Emmons−Horner reaction of **19** with C2-cyanophosphonate, produced ethyl 11*Z*,13*E*-retinonitrile−tricarbonyliron complex **21** as the only product. Decomplexation of **21** with $CuCl_2$ and subsequent DIBAL reduction gave 11*Z*-retinal **2** in excellent yield. Mechanistic consideration of *Z*-selectivity in the Peterson reaction of the aldehyde−tricarbonyliron complex is also discussed.

It is well-known that retinal **1** is a chromophore of photosensitive pigments such as rhodopsin, bacteriorhodopsin, retinochrome, and so on. These pigments covalently bond to the retinal through a protonated Schiff base with lysine of the protein opsin and play an important role as retinal proteins in vital cells. The most characteristic feature of these compounds is that the biological activities are dependent upon the stereochemistry of the retinal in the protein. For example, the chromophore of the visual pigment rhodopsin is 11*Z*-retinal **2** and those of bacteriorhodopsin and retinochrome, whose functions are a light-driven proton pump and a regeneration of rhodopsin, are 13*Z*- and *all-E*-retinals, respectively.[1,2] Although there are a number of reports available in the literature for the synthesis of retinal and related compounds to investigate the biological function of these proteins, only a few reports for the stereoselective synthesis[3] have been found, except for the *all-E* isomer. Recently, we have developed a novel method for a stereoselective synthesis of *all-E* and 9*Z*-retinoic acids using the tricarbonyliron complex.[4] In continuation of our study torward the synthesis of retinal and related compounds, herein we describe a stereoselective synthesis of 11*Z*-retinal from the *β*-ionylideneacetaldehyde−tricarbonyliron complex, including the full account of our work in the preliminary communication[5] (Figure 1)

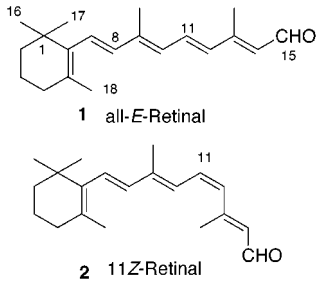

Figure 1. Structure of retinals.

Results and Discussion

Construction of the *Z*-stereochemistry in a disubstituted olefin is essential for the preparation of 11*Z*-retinal. To achieve this, there are various methods such as selective hydrogenation of the acetylene compounds,[6] olefination of the aldehyde using phosphonate reagent having a fluorine atom,[7] and a cross-coupling reaction of vinyl halides with metal olefins in the presence of a palladium catalyst.[8] However, these methods are not satisfactory for the preparation of 11Z-retinal **2** due to the low yield, low stereoselectivity, and a difficulty in the synthesis of the starting materials. Recently, it was shown that the aldol condensation of aldehyde having the arene−tricarbonylchromium complex[9] or alkyne−hexacarbonyldicobalt complex[10] with silyl enol ether or silyl ketene acetal exhibits a different stereoselectivity compared to that of the uncomplexed aldehydes. We also found that in the dehydration of ethyl acetate adduct of

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

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(6) Oroshnik, W. *J. Am. Chem. Soc.* **1956**, *78*, 2651.

(7) (a) Mead, D.; Asato, A. E.; Denny, M.; Liu, R. S. H.; Hanzawa, Y., Taguchi, T.; Yamada, A.; Kobayashi, N.; Hosoda, A.; Kobayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 259. (b) Trehan, A.; Liu, R. S. H. *Tetrahedron Lett.* **1988**, *29*, 419.

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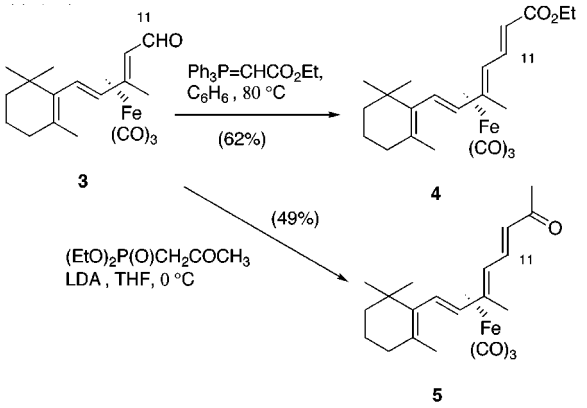
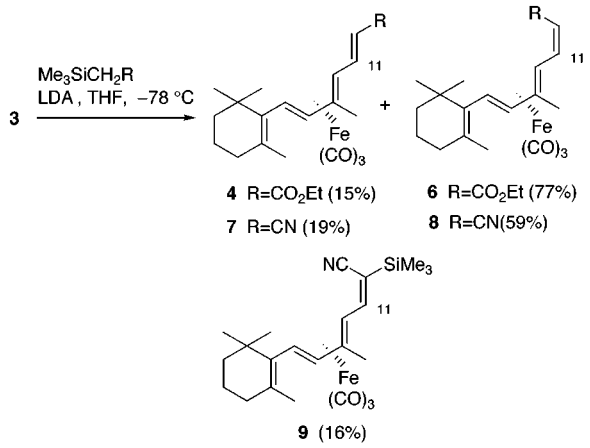
Scheme 1



Scheme 2



β-ionone−tricarbonyliron complex by thionyl chloride, the *Z*-olefin was predominantly produced in contrast to the usual dehydration, in which the thermodynamically most stable *E*-olefin was preferentially produced via the E_1-mechanism.[11] These findings suggested us that the aldehyde−tricarbonyliron complex is a strong candidate for the construction of disubstituted *Z*-olefin and it would be a useful substrate for the preparation of 11*Z*-retinal **2**.

First, we attempted numerous olefination reactions of the β-ionylideneacetaldehyde−tricarbonyliron complex **3**,[4b] which was easily derived from the β-ionone−tricarbonyliron complex by the reaction of the lithium salt of acetonitrile followed by DIBAL reduction. The Wittig reaction or the Emmons−Horner reaction of **3** using triphenylcarbethoxymethylene−phosphorane or diethyl (2-oxopropyl)phosphonate afforded the *E*-olefinic products **4** and **5** as the sole products in 62% and 49% yields, respectively (Scheme 1). The geometry of the newly produced double bond at the 11 position in **4** and **5** was determined as *E* from their NMR spectra, in which the coupling constants between the 11 and 12 positions exhibited 15 and 15.5 Hz, respectively.[12] In the reaction of **3** with acetone under the basic conditions, the aldehyde−tricarbonyl complex **3** was recovered unchanged.

On the contrary, treatment of **3** with the lithium enolate of ethyl trimethylsilylacetate in THF at −70 °C afforded the *Z*-isomer **6** predominantly (77%) accompanied by the 11*E*-isomer **4** (15%). Similarly, in the reaction of trimethylsilylacetonitrile, the 11*Z*-nitrile **8** (59%) was obtained as the major product in addition to the 11*E*-isomer **7** (19%) and trimethylsilylnitrile **9** (16%), which seemed to be produced by dehydration from the reaction intermediate. The structure of **9** was determined by desilylation with tetrabutylammonium fluoride in THF to yield **8**. As the interconversion of the *Z*-ester **6** to the *E*-ester **4** was not found under the reaction conditions used, we speculated that the stereoselectivity is controlled by formation of kinetically preferred β-hydroxysilane, which is followed by a synchronous syn elimination[13] (Scheme 2).

To confirm the generality of this *Z*-stereoselectivity, the Peterson reaction of various aldehyde−tricarbonyliron complexes was investigated. The substrates **11a**−**c** were easily prepared from the tricarbonyliron-complex **10a**−**c**[14] by the reaction of the lithium salt of acetonitrile and subsequent DIBAL reduction.[15] In these reactions, a similar migration of tricarbonyliron was observed as shown for the preparation of **3**.[4b] The Peterson reaction of ethyl and isopropyl derivatives **11b**,**c** smoothly proceeded to give predominantly *Z*-isomers **13b**,**c** in 58% and 56% yields, respectively. The increase in the bulkiness of the 9-substituent caused a slight decrease in the yield of the products; however, the *Z*-stereoselectivity was not seriously affected. In the case of **11a**, which had no alkyl substituent at the 9-position, the *Z*-stereoselectivity was dramatically decreased, and almost the same amount of *E*- and *Z*-isomers was obtained. Furthermore, when the noncomplexed aldehyde **14** was treated with ethyl trimethylsilylacetate, the *E*-isomer **15** was obtained as the major product (60%) accompanied by the *Z*-isomer **16** in 38% yield (Scheme 3).

These facts strongly suggest that both the tricarbonyliron complex and the 9-substituent are essential for the *Z*-stereoselectivity during these Peterson reactions. Although the mechanism for this high *Z*-selectivity is not clear yet, we tentatively propose the following explanation. It is well-known that in the dienylaldehyde−tricarbonyliron complex the carbonyl group of the aldehyde exists in both the s-cis and s-trans conformations around the $C_{10}-C_{11}$ single bond.[16] However, if there is a substituent at the 9-position such as **3** and **11b**,**c**, the carbonyl group would have the s-trans conformation in order to avoid the steric interaction between the carbonyl group of the aldehyde with the C_9-substituent (Figure 2).[17]

There are six possible transition states, in which the lithium enolate approaches the aldehyde from the opposite side of the tricarbonyliron complex[18] (Scheme 4). Among these transition states, transition states [A1] and [B3] may be favorable due to the steric repulsion between

(11) Lomas, J. S.; Sagatys, D. S.; Dubois, J. E. *Tetrahedron Lett.* **1971**, 599.

(12) For structural comparisons standard retinoid numbering has been used.

(13) Hudrlik, P. F.; Peterson, D., Rona, R. J. *J. Org. Chem.* **1975**, *40*, 2263.

(14) Wada, A.; Fujioka, N.; Ito, M. *Chem. Pharm. Bull.* **1999**, *47*, 171.

(15) In the case of **10c**, the *Z*-iosmer of **11c** was also obtained in 25% yield.

(16) Grée, R. *Synthesis* **1989**, 341.

(17) X-ray analysis of **3** exhibits the s-trans conformation of the carbonyl group of the aldehyde, and this result will be published in near future. In the NMR NOE experiment of compound **3**, both cross-peaks between the aldehyde proton and C_{10}-proton (s-cis conformation) or C_9-methyl protons (s-trans conformation) were observed; therefore, it was impossible to confirm the conformation of the carbonyl group by NMR.

(18) Clinton, N. A.; Lillya, C. P. *J. Am. Chem. Soc.* **1970**, *92*, 3058.

Scheme 3

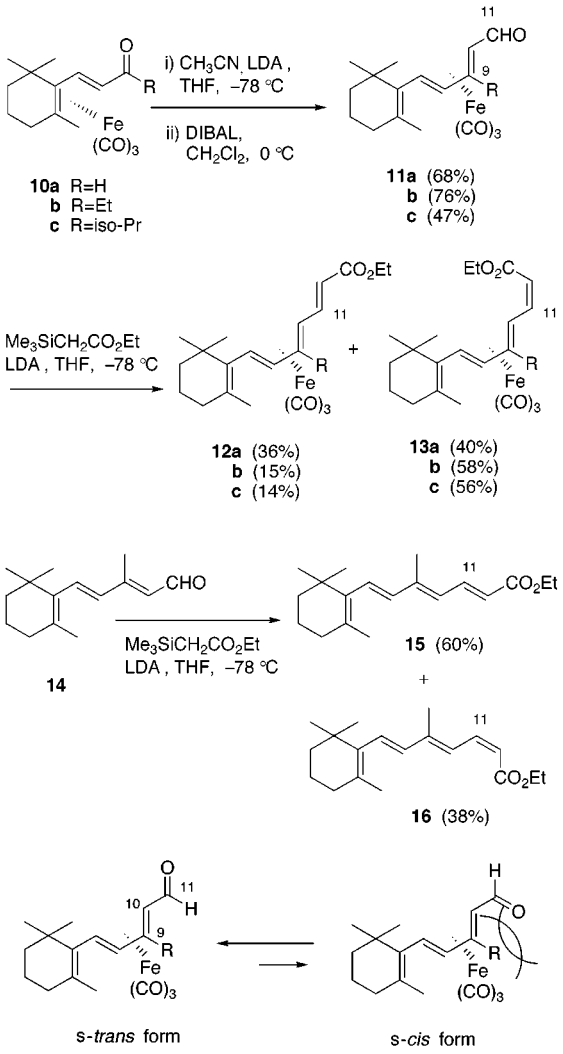
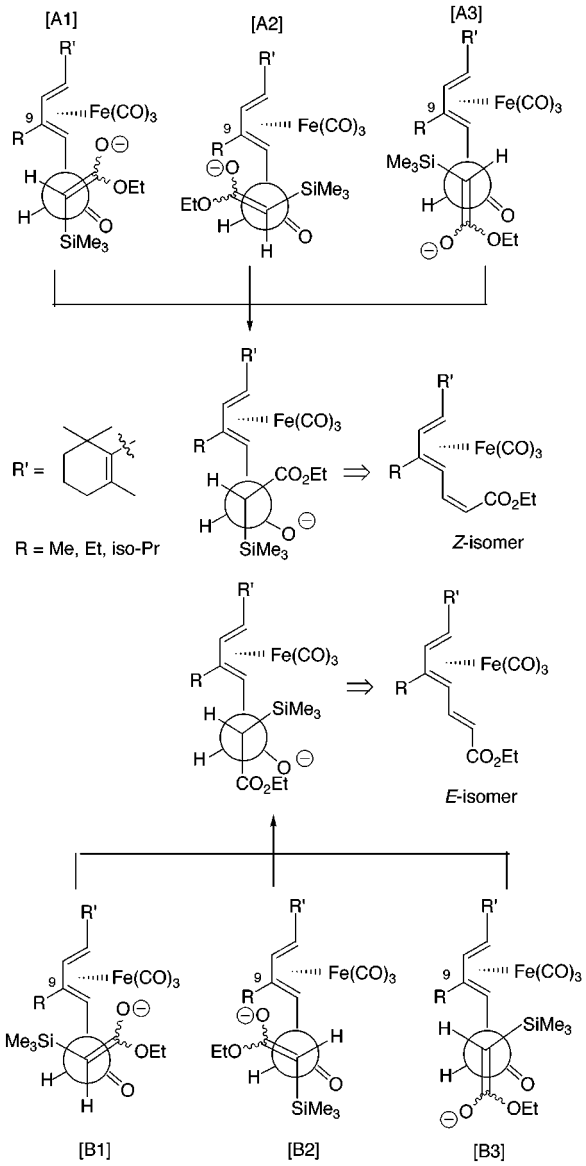


Figure 2. Conformation of dienylaldehyde−tricarbonyliron complex.

Scheme 4



the 9-alkyl group and the substituent on the enolate. Thus, in these transition states the hydrogen occupied the least-hindered position in the reaction intermediate. In these two transition states, [B3] has a serious interaction between the trimethylsilyl group and the diene−tricarbonyliron complex compared with that of [A1]. Therefore, the transition state [A1] was preferred to afford the *Z*-olefin via syn elimination from the *β*-hydroxysilyl adduct.[13]

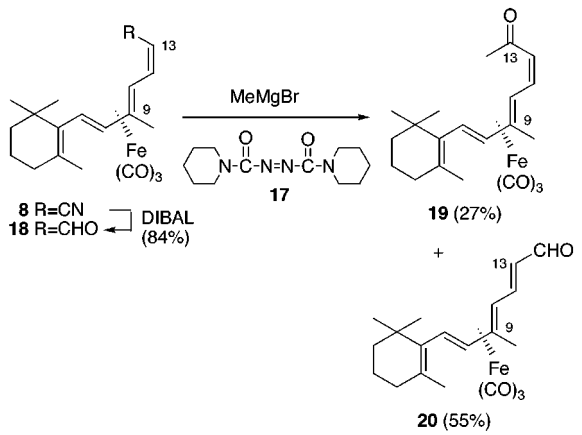
According to the above hypothesis, the more bulky silyl substituent on the Peterson reagent seems to afford the higher *Z*-selectivity in the olefin products. Indeed, in the reaction of the aldehyde−tircarbonyliron complex **3** with *tert*-butyldimethylsilylacetonitrile, the *Z*-olefin **8** was obtained exclusively in 30% yield, and this fact strongly supports our proposed reaction mechanism, although the yield of product was low due to the steric bulkiness of the reagent.

Subsequently, we focused our attention on the transformation of the ester **6** or nitrile **8** to 11*Z*-retinal **2**. A direct conversion of the nitrile **8** to the C18-ketone−tricarbonyliron complex **19** using methylmagnesium bromide was unsuccessful. Recently, we have succeeded in converting the aldehyde−tricarbonyliron complex to the ketone−tricarbonyliron complex without decomplexation by the reaction with the Grignard reagent and subsequent oxidation of magnesium salt by Mukaiyama's method[19] using 1,1′-(azodicarbonyl)dipiperidine **17**.[4b] To apply this methodology, the nitrile **8** was converted to the aldehyde−tricarbonyliron complex **18** by DIBAL reduction in 84% yield. Treatment of **18** with methylmagnesium bromide followed by oxidation with **17** afforded the desired ketone **19** and isomerized aldehyde **20** in 27% and 55% yields, respectively. These structures were determined on the basis of their spectral data. The aldehyde **20** seemed to be formed by isomerization of the starting aldehyde **18** under the basic reaction conditions used, and it is evident that the rate of isomerization was faster than that of the oxidation of the magnesium salt, which was generated by the addition of methylmagnesium bromide to the aldehyde **18**, since the isomerized aldehyde **20** was obtained as the major product (Scheme 5).

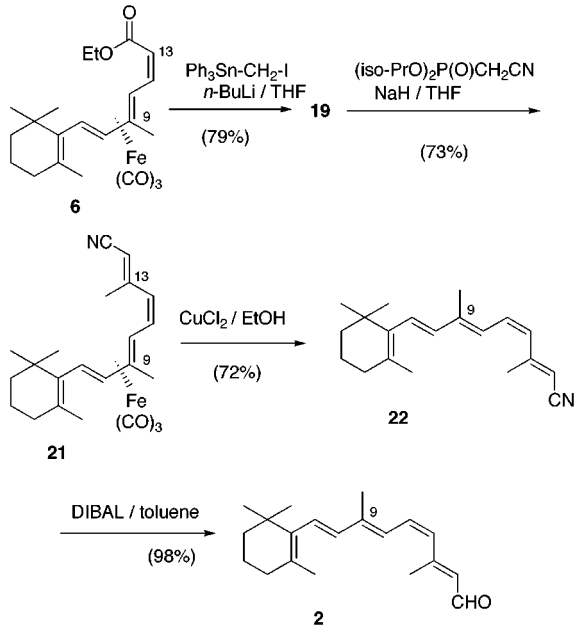
On the other hand, the conversion of the ester **6** to **19** by the reported method using triphenylstannylmethyl-

(19) Saigo, K.; Morikawa, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1656.

Scheme 5



Scheme 6



lithium[20] smoothly proceeded to give the desired ketone **19** in excellent yield. The Emmons−Horner reaction of **19** with diisopropyl cyanomethylphosphonate using sodium hydride as base gave the nitrile **21** as the single product in 73% yield. After decomplexation of **21** with copper(II) dichloride,[21] the final transformation of **22** to the 11*Z*-retinal **2** was achieved by DIBAL reduction in good yield (Scheme 6).

In summary, we have developed a new method for stereoselective *Z*-olefin synthesis by the Peterson reaction of the aldehyde tricarbonyliron complex and also achieved the stereoselective synthesis of 11*Z*-retinal **2** by applying this methodology. This method would provide a novel route for the stereoselective synthesis of vitamin A and related compounds.

Experimental Section

All melting points are uncorrected. UV−vis spectra were recorded in ethanol, IR spectra in chloroform, and ^{1}H NMR spectra in deuteriochloroform unless otherwise stated at 200, 300, or 500 MHz. Column chromatography (CC) under reduced pressure by aspirator was performed using Merck silica gel 60. Medium pressure CC was carried out using Merck LiChroprep Si 60. All reactions were carried out under a nitrogen atmosphere. THF and ether were purified by distillation from benzophenone-sodium ketyl under nitrogen. Standard workup means that the organic layers were finally washed with brine, dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated in vacuo below 30 °C using a rotary evaporator.

Tricarbonyl [Ethyl (η^4-4,5,6,7)-(2*E*,4*E*,6*E*)-5-Methyl-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6-heptatrienoate]-iron(0) (4). A mixture of β-iononylideneacetaldehyde tricarbonyliron complex **3** (100 mg, 0.28 mmol) and (carbethoxymethylene)triphenylphosphorane (118 mg, 0.34 mmol) in benzene (20 mL) was heated under reflux for 6 h. After cooling, the solvent was removed in vacuo, and the residue was purified by CC (ether/hexane 1:9) to give the ester **4** (74.6 mg, 62%) as an orange oil: UV−vis 322, 247 nm (sh); IR 2933, 2056, 1995, 1703 cm^{-1}; ^{1}HNMR (300 MHz) δ 1.15 (s, 3H), 1.26 (s, 3H), 1.29 (t, J = 7 Hz, 3H), 1.4−1.62 (m, 4H), 1.56 (d, J = 11 Hz, 1H), 1.81 (s, 3H), 1.97−2.09 (m, 2H), 2.11 (d, J = 11 Hz, 1H), 2.4 (s, 3H), 4.19 (q, J = 7 Hz, 2H), 5.72 (d, J = 11 Hz, 1H), 5.98 (d, J = 15 Hz, 1H), 7.09 (dd, J = 15, 11 Hz, 1H); ^{13}C NMR (125 MHz) δ 14.3, 18.9, 20.1, 23.0, 28.8, 29.8, 34.9, 35.2, 42.2, 56.9, 60.2, 62.6, 86.1, 97.3, 119.2, 135.0, 135.4, 145.8, 166.7, 211.8 (C3); HRMS calcd for $C_{22}H_{28}FeO_5$ 428.1287, found 428.1295 (M$^-$).

Tricarbonyl [(η^4-5,6,7,8)-(3*E*,5*E*,7*E*)-6-Methyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3,5,7-octatrien-2-one]iron-(0) (5). To a stirred solution of diethyl(2-oxopropyl)phosphonate (97 mg, 0.6 mmol) in THF (5 mL) was added a solution of *n*-butyllithium (1.6 M hexane solution, 0.38 mL, 0.6 mmol) at 0 °C. After the mixture was stirred for 30 min, a solution of the β-iononylideneacetaldehyde tricarbonyliron complex **3** (70 mg, 0.2 mmol) in THF (5 mL) was added. The resulting mixture was stirred for an additional 5 h at rt. After addition of saturated aqueous NH_4Cl and evaporation of the solvent, the organics were extracted with ether followed by standard workup. The residue was purified by CC (ether/hexane 1:4) to give the ketone **5** (37.9 mg, 49%) as an orange oil: UV−vis 297 nm; IR 2979, 2040, 1979, 1655, 1591 cm^{-1}; ^{1}H NMR (300 MHz) δ: 1.16 (s, 3H), 1.27 (s, 3H), 1.4−1.6 (m, 4H), 1.56 (d, J = 11 Hz, 1H), 1.83 (s, 3H), 2.02 (br t, J = 6.5 Hz, 2H), 2.18 (d, J = 11 Hz, 1H), 2.24 (s, 3H), 2.42 (s, 3H), 5.76 (d, J = 11 Hz, 1H), 6.28 (d, J = 15.5 Hz, 1H), 6.97 (dd, J = 15.5, 11 Hz, 1H); HRMS calcd for $C_{21}H_{26}FeO_4$ 398.1182, found 398.1191 (M$^-$).

Tricarbonyl [Ethyl (η^4-4,5,6,7)-(2*E*,4*E*,6*E*)-5-Methyl-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6-heptatrienoate]-iron(0) (4) and Tricarbonyl [Ethyl (η^4-4,5,6,7)- (2*Z*,4*E*,6*E*)-5-Methyl-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6-heptatrienoate]iron(0) (6). To a solution of LDA, prepared from *n*-butyllithium (1.6 M hexane solution, 1.93 mL, 3.08 mmol) and diisopropylamine (0.43 mL, 3.08 mmol) in THF (30 mL), was added a solution of ethyl trimethylsilylacetate (0.56 mL, 3.08 mmol) at −78 °C, and the resulting mixture was stirred for an additional 20 min. A solution of the aldehyde **3** (1 g, 2.79 mmol) in THF (10 mL) was added at −78 °C, and the mixture was further stirred for 20 min. The reaction was quenched with saturated aqueous NH_4Cl and then extracted with ether followed by standard workup. The residue was purified by CC (ether/hexane 1:4) to give the esters of **4** (180 mg, 15%) and **6** (923 mg, 77%) as an orange oil, respectively. The *E*-ester **4** was identical with the authentic specimen obtained by the previous method.

11*Z*-Isomer 6: UV−vis 280 nm; IR 2935, 2041, 1980, 1699, 1614 cm^{-1};^{1}H NMR (300 MHz) δ 1.17 (s, 3H), 1.28 (s, 3H), 1.29 (t, J = 7 Hz, 3H), 1.4−1.62 (m, 4H), 1.86 (s, 3H), 1.97−2.09 (m, 2H), 2.34 (d, J = 11 Hz, 1H), 2.37 (s, 3H), 3.36 (d, J = 11 Hz, 1H), 4.19 (q, J = 7 Hz, 2H), 5.50 (d, J = 11 Hz, 1H), 5.71 (d, J = 11 Hz, 1H), 6.39 (t, J = 11 Hz, 1H); ^{13}C NMR (125 MHz) δ 14.4, 18.9, 19.4, 23.1, 28.9, 29.9, 34.9, 35.1, 42.2, 54.1, 59.9, 63.0, 86.4, 97.8, 116.1, 135.1, 135.3, 145.8, 166.8, 212.0 (C3); HRMS calcd for $C_{22}H_{28}FeO_5$ 428.1287, found 428.1293 (M$^-$).

(20) Sato, T.; Matsuoka, H., Igarashi, T.; Minomura, M.; Murayama, E. *J. Org. Chem*. **1988**, *53*, 1207.
(21) Pearson, A. J.; Lai, Y. S.; Lu, W.; Pinkerton, A. A. *J. Org. Chem*. **1989**, *54*, 3882.

Tricarbonyl [(η^4-4,5,6,7)-(2*E*,4*E*,6*E*)-5-Methyl-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6-heptatrienenitrile]iron-(0) (7), Tricarbonyl [(η^4-4,5,6,7)-(2*Z*,4*E*,6*E*)-5-Methyl-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6-heptatrienenitrile]iron(0) (8), and Tricarbonyl [(η^4-4,5,6,7)-(2*E*,4*E*,6*E*)-5-Methyl-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-trimethylsilyl-2,4,6-heptatrienenitrile]iron(0) (9). In the same manner as described for the preparation of **4** and **6**, the tricarbonyliron complex **3** (1.0 g, 2.79 mmol) was reacted with trimethylsilylacetonitrile (0.35 mL, 2.52 mmol). The residue was purified by medium-pressure CC (ether/hexane 1:4) to give the nitriles **7** (61 mg, 19%), **8** (188 mg, 59%), and **9** (60 mg, 16%) as an orange solid, respectively.

11*E*-Isomer 7: mp 109−111 °C (ether−*n*-hexane); UV−vis 281 nm; IR 2936, 2216, 2042, 1981, 1605 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.14 (s, 3H), 1.25 (s, 3H), 1.4−1.6 (m, 4H), 1.44 (d, J = 11 Hz, 1H), 1.81 (s, 3H), 2.01 (br t, J = 6 Hz, 2H), 2.17 (d, J = 11 Hz, 1H), 2.36 (s, 3H), 5.41 (d, J = 16 Hz, 1H), 5.73 (d, J = 11 Hz, 1H), 6.77 (dd, J = 16, 11 Hz, 1H); HRMS calcd for $C_{20}H_{23}FeNO_3$ 381.1028, found 381.1038 (M^-).

11*Z*-Isomer 8: mp 108−110 °C (ether−*n*-hexane); UV−vis 280 nm; IR 2935, 2213, 2042, 1984, 1593 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.16 (s, 3H), 1.27 (s, 3H), 1.4−1.6 (m, 4H), 1.85 (s, 3H), 1.89 (d, J = 11 Hz, 1H), 2.02 (br t, J = 6 Hz, 2H), 2.37 (s, 3H), 2.41 (d, J = 11 Hz, 1H), 5.14 (d, J = 11 Hz, 1H), 5.74 (d, J = 11 Hz, 1H), 6.60 (t, J = 11 Hz, 1H); HRMS calcd for $C_{20}H_{23}FeNO_3$ 381.1028, found 381.1033 (M^-).

Trimethylsilyl compound 9: mp 93−96 °C (ether−*n*-hexane); UV−vis 291 nm; IR 2933, 2192, 2041, 1983, 1566 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.23 (s, 9H), 1.16 (s, 3H), 1.27 (s, 3H), 1.4−1.6 (m, 4H), 1.85 (s, 3H), 2.08 (br t, J = 6 Hz, 2H), 2.12 (d, J = 11 Hz, 1H), 2.38 (s, 3H), 2.44 (d, J = 11 Hz, 1H), 5.73 (d, J = 11 Hz, 1H), 6.66 (d, J = 11 Hz, 1H); HRMS calcd for $C_{23}H_{31}FeNO_3Si$ 453.1424, found 453.1411 (M^-).

Conversion of 9 to 8. To a stirred solution of silylnitrile **9** (59 mg, 0.13 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (0.03 mL, 0.13 mmol) at 0 °C, and the resulting mixture was stirred for an additional 10 min. The reaction was quenched with saturated NH_4Cl, and then the reaction mixture was extracted with ether followed by standard workup. The residue was purified by CC (ether/benzene/hexane 1:2:7) to give the nitrile **8** (48 mg, 96%). This was identical with the authentic specimen obtained by the previous method.

Tricarbonyl[(η^4-4,5,6,7)-(2*Z*,4*E*,6*E*)-5-Methyl-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6-heptatrienal]iron(0) (18). To a solution of the nitrile **8** (200 mg, 0.52 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise a solution of DIBAL (0.12 mL, 0.68 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C. After the solution was stirred for an additional 30 min at 0 °C, the excess DIBAL was destroyed by addition of moist silica gel (H_2O/SiO_2 1:5). After filtration with Celite, the filtrate was dried over Na_2SO_4. The solvent was evaporated off, and the residue was purified by CC (ether/hexane 1:4) to afford the aldehyde **18** (168 mg, 84%) as a red oil: UV−vis 294 nm; IR 2935, 2042, 1982, 1673, 1608 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 1.16 (s, 3H), 1.28 (s, 3H), 1.3−1.5 (m, 4H), 1.72 (s, 3H), 1.80 (br t, J = 6 Hz, 2H), 1.81 (s, 3H), 2.32 (d, J = 11 Hz, 1H), 2.79 (d, J = 11 Hz, 1H), 5.49 (d, J = 11 Hz, 1H), 5.59 (dd, J = 11, 4.5 Hz, 1H), 6.11 (t, J = 11 Hz, 1H), 9.83 (d, J = 4.5 Hz, CHO); HRMS calcd for $C_{20}H_{24}FeO_4$ 384.1025, found 384.1041 (M^-).

Tricarbonyl[(η^4-5,6,7,8)-(3*Z*,5*E*,7*E*)-6-Methyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3,5,7-octatrien-2-one]iron-(0) (19) and Tricarbonyl[(η^4-4,5,6,7)-(2*E*,4*E*,6*E*)-5-Methyl-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6-heptatrienal]iron(0) (20). To a solution of the aldehyde **18** (100 mg, 0.26 mmol) in dry Et_2O (5 mL) was added isopropylmagnesium bromide (1M ether solution, 0.34 mL, 0.34 mmol) at 0 °C, and the resulting mixture was stirred for an additional 30 min. A solution of 1,1-(azodicarbonyl)dipiperidine (78.7 mg, 0.31 mmol) in THF (5 mL) was added at 0 °C. After addition of saturated aqueous NaCl (10 mL) and evaporation of the solvent, the organics were extracted with ether and washed with saturated aqueous $NaHCO_3$. The residue was purified by CC (ether/benzene/hexane 1:2:11) to give the ketone **19** (28 mg, 27%) and aldehyde **20** (60 mg, 60%) as a red oil, respectively.

Ketone 19: UV−vis 290 nm; IR 2933, 2039, 1979, 1673, 1576 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 1.21 (s, 3H), 1.33 (s, 3H), 1.3−1.5 (m, 4H), 1.80 (br t, J = 6.5 Hz, 2H), 1.83 (s, 6H), 1.90 (s, 3H), 2.59 (d, J = 11 Hz, 1H), 3.80 (d, J = 11 Hz, 1H), 5.53 (d, J = 11 Hz, 1H), 5.60 (d, J = 11 Hz, 1H), 6.05 (t, J = 11 Hz, 1H); ^{13}C NMR (125 MHz) δ 18.9, 19.1, 23.1, 28.9, 29.9, 31.7, 34.9, 35.2, 42.2, 54.7, 63.7, 86.5, 98.4, 122.3, 135.1, 135.5, 145.1, 198.6, 211.9 (C3); HRMS calcd for $C_{21}H_{26}FeO_4$ 398.1182, found 398.1166 (M^-).

Aldehyde 20: UV−vis 295 nm; IR 2935, 2041, 1981, 1664 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 1.13 (s, 3H), 1.15 (d, J = 11 Hz, 1H), 1.25 (s, 3H), 1.3−1.5 (m, 4H), 1.68 (s, 3H), 1.80 (s, 3H), 1.81 (br t, J = 6 Hz, 2H), 2.02 (d, J = 11 Hz, 1H), 5.48 (d, J = 11 Hz, 1H), 6.10 (dd, J = 15, 7.5 Hz, 1H), 6.50 (dd, J = 15, 11 Hz, 1H), 9.29 (d, J = 7.5 Hz, 1H); HRMS calcd for $C_{20}H_{24}FeO_4$ 384.1025, found 384.1025 (M^-).

Conversion of 6 to 19. To a stirred solution of Ph_3SnCH_2I (688 mg, 1.4 mmol) in dry Et_2O (20 mL) was added a solution of *n*-butyllithium (1.6 M hexane solution, 0.88 mL, 1.4 mmol) at −50 °C, and the resulting mixture was stirred for an additional 10 min. A solution of the ester **6** (200 mg, 0.47 mmol) in dry Et_2O (5 mL) was added at −78 °C, and the mixture was stirred for 2 h at −78 °C. After addition of saturated aqueous NaCl (10 mL) and evaporation of the solvent, the organics were extracted with ether followed by standard workup. The residue was purified by CC (ether/hexane 1:4) to give the ketone **19** (148 mg, 79%) as an orange oil. This compound **19** was identical with the authentic specimen obtained by the previous method.

Tricarbonyl[(η^4-6,7,8,9)-(2*E*,4*Z*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenenitrile]iron(0) (21). To a solution of sodium hydride (60% oil dispersion, 40 mg, 1 mmol) in THF (5 mL) was added dropwise diisopropylcyanomethylphosphonate (0.2 mL, 1 mmol) at 0 °C. After the solution was stirred for an additional 30 min at rt, a solution of the ketone **19** (80 mg, 0.2 mmol) in THF (4 mL) was added at 0 °C. After the solution was stirred for an additional 24 h at rt, the reaction was quenched with saturated aqueous NH_4Cl and then extracted with ether followed by standard workup. The residue was purified by CC (ether/hexane 1:9) to give **21** (62 mg, 73%) as a red oil: UV−vis 317 nm; IR 2934, 2211, 2036, 1973, 1598 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 1.16 (s, 3H), 1.27 (s, 3H), 1.3−1.5 (m, 4H), 1.68 (s, 3H), 1.74−1.82 (m, 2H), 1.85 (d, J = 10.5 Hz, 1H), 1.88 (s, 3H), 1.95 (s, 3H), 2.02 (d, J = 11 Hz, 2H), 4.82 (s, 1H), 5.28 (d, J = 12 Hz, 1H), 5.51 (d, J = 11 Hz, 1H), 5.58 (br t, J = 12 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 19.1, 19.2, 20.6, 23.0, 29.0, 29.8, 35.0, 35.2, 42.4, 56.2, 63.2, 85.7, 96.5, 99.6, 117.3, 127.6, 134.5, 135.1, 136.0, 156.6, 212.7 (C3); HRMS calcd for $C_{23}H_{27}FeNO_3$ 421.1389, found 421.1354 (M^-).

(2*E*,4*Z*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenenitrile (22). To a stirred solution of nitrile complex **21** (19 m g, 0.045 mmol) in ethanol (2 mL) was added a solution of copper(II) chloride (30 mg, 0.23 mmol) in ethanol (3 mL) at rt, and the resulting mixture was stirred for an additional 30 min. After removal of ethanol, the residue was extracted with ether followed by standard workup. The residue was purified by CC (ether/hexane 1:9) to give the decomplexed nitrile **22** (9.4 mg, 72%) as a pale yellow oil. The ^{1}H NMR spectrum is consistent with that of the literature.[22]

(2*E*,4*Z*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenal (2). To a solution of nitrile **22** (9 mg, 0.032 mmol) in dry toluene (5 mL) was added dropwise DIBAL (0.0074 mL, 0.042 mmol) in dry toluene (0.2 mL) at 0 °C. After stirring for an additional 30 min at 0 °C, the excess DIBAL was destroyed by addition of moist silica gel (H_2O/SiO_2 1:5). After removal of toluene, the residue was extracted with ether followed by standard workup. The residue

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was purified by CC (ether/hexane 1:9) to give the aldehyde **2** (9 mg, 98%) as a yellow oil. The ^{1}H NMR spectrum is consistent with that of the literature.[23]

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Supporting Information Available: Experimental procedures for **11**−**13**, **15**, and **16**, ^{1}H NMR spectra for compounds **4**−**9**, **12a**, **13a**, and **18**−**21**, and ^{13}C NMR spectra for compounds **4**, **6**, **19,** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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