A Novel Method for a Stereoselective Synthesis of Trisubstituted Olefin Using Tricarbonyliron Complex: A Highly Stereoselective Synthesis of (*all-E*)- and (9*Z*)-Retinoic Acids†

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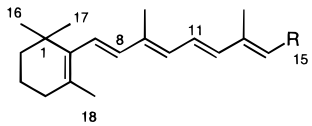
Received June 3, 1996⊗

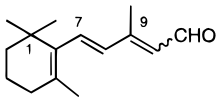
In order to establish the stereoselective synthesis of retinoic acids, which are ligand molecules of the retinoic acid receptors (RARs, all-*E*-isomer) and the retinoid X receptors (RXRs, 9*Z*-isomer), the reaction of β-ionone−tricarbonyliron complex **7** with carbanions was investigated. Treatment of **7** with the lithium salt of acetonitrile afforded (7*E*,9*E*)-β-ionylideneacetonitrile−tricarbonyliron complex **8** exclusively, *via* addition, dehydration, and migration of tricarbonyliron complex. On the contrary, the reaction of **7** with the lithium enolate of ethyl acetate and subsequent dehydration by thionyl chloride afforded the ethyl (7*E*,9*Z*)-β-ionylideneacetate−tricarbonyliron complex **16b** predominantly. These compounds (**8** and **16b**) were converted to the corresponding β-ionylideneacetaldehyde−tricarbonyliron complexes (**10** and **22**) in excellent yields, respectively. The Emmons−Horner reaction of these compounds with C5-phosphonate followed by the sequence of decomplexation and alkaline hydrolysis gave the corresponding retinoic acids (**26** and **29**).

Retinoids **1** are covalently or noncovalently bound to proteins and play an important role as retinoid proteins in vital cells. The most characteristic feature of these compounds is that the biological activities depend upon the stereochemistry of retinoid in the protein. For example, the chromophore of the visual pigment rhodopsin is (11*Z*)-retinal[1] and those of bacteriorhodopsin and retinochrome, which function as a light-driven proton pump and for regeneration of rodopsin, are (13*Z*)- and (*all-E*)-retinals, respectively.[2] In addition, it has been recently established that retinoic acids play fundamental roles in cell differentiation and proliferation through modulation of their intracellular retinoid receptors. These receptors comprise two distinct classes, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs), which have (*all-E*)- and (9*Z*)-retinoic acids as ligand molecules, respectively.[3]

In contrast to the recognition of the significance of the configuration of retinoids, little is known about the stereoselective synthesis of geometrical isomers of retinoids. Therefore, high-performance liquid chromatography (HPLC) is a powerful tool to obtain pure stereoisomers from an isomeric mixture of retinoids. However, it is not suitable for large-scale preparation. In this report, we describe the full account of a previous communication[4] on the stereoselective synthesis of (7*E*,9*E*)- and (7*E*,9*Z*)-β-ionylideneacetaldehydes[5] (**2a** and **2b**) using a tricarbonyliron complex and its application to the synthesis of retinoic acids.



1 R=CHO Retinal
R=CO_2H Retinoic acid



2a : 9*E*
b : 9*Z*

Results and Discussion

The conversion of carbonyl compounds to α,β-unsaturated aldehydes is an important reaction in organic synthesis. For this conversion there are a number of methods such as Aldol condensation,[6] Wittig reaction,[7] Peterson olefination,[8] Emmons−Horner reaction,[9] etc. However, there are few methods that can be applied to the stereoselective synthesis of retinoid and related compounds. Especially, the stereoselective synthesis of trisubstituted olefins is the most difficult unsolved problem in this field. Thus, β-ionylideneacetaldehyde **2** possessing a trisubstituted olefin is a very important material for the synthesis of retinoids and carotenoids,[10]

† Retinoids and Related Compounds. 21. For part 20, see: Wada, A.; Sakai, M.; Imamoto, Y.; Shichida, Y.; Yamauchi, M.; Ito, M. *J. Chem. Soc., Perkin Trans. 1.* In press.

‡ Kobe Pharmaceutical University.

§ Tanabe Seiyaku Co., Ltd.

⊗ Abstract published in *Advance ACS Abstracts,* May 15, 1997.

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(7) (a) For reviews, see: Maercker, A. *Org. React.* **1965**, *14*, 270. (b) Trippett, S. *Q. Rev.* **1963**, *17*, 406.

(8) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. (b) For reviews, see: Ager, D. J. *Synthesis* **1984**, 384. (c) Ager, D. J. *Org. React.* **1990**, *28*, 1.

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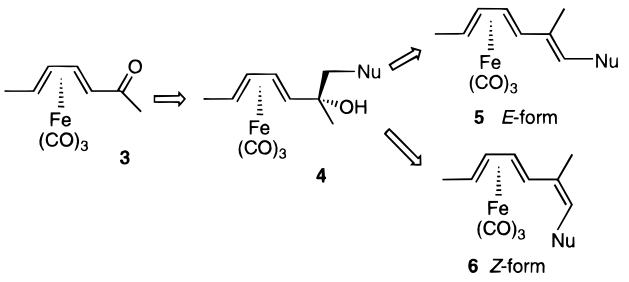
S0022-3263(96)01041-9 CCC: $14.00

Scheme 1

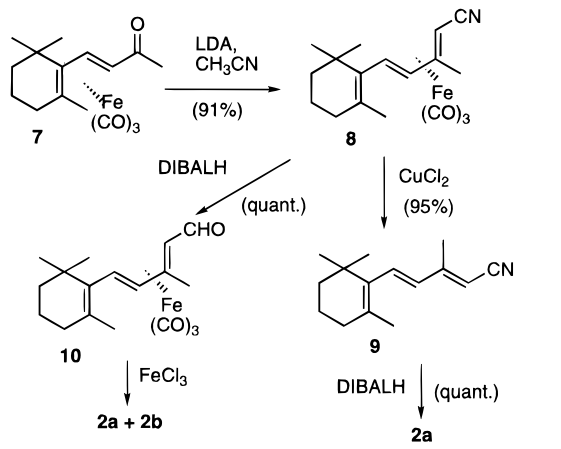


and although there have been a number of reports dealing with the synthesis of **2**,[11] no stereoselective syntheses of **2** has been reported.

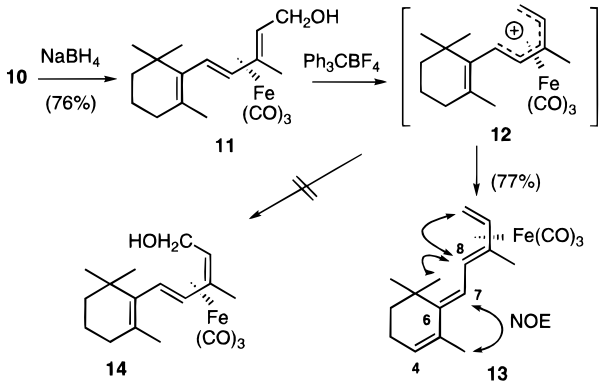
In these circumstances, we investigated the possibility of utilizing diene−tricarbonyliron complexes for the synthesis of biologically interesting polyolefins. These complexes have found numerous applications in organic synthesis due to their ease of preparation, resolution, and diastereoselective reactivity.[12] If the stereocontrolled formation of a double bond is possible by dehydration of the adduct **4**, easily obtained from the reaction of the dienyl methyl ketone−tricarbonyliron complex **3** with nucleophiles, as shown in Scheme 1, it would provide a new method for the stereoselective synthesis of trisubstituted olefins **5** and **6**. These compounds have the partial structures of (9*E*)- and (9*Z*)-ionylideneacetaldehydes **2a**,**b** and would be transformed to the corresponding polyolefinic compounds such as retinoic acids. We employed β-ionone−tricarbonyliron complex **7** as the starting material for this study.

Although β-ionone−tricarbonyliron complex **7** is a known compound,[13] we obtained **7** more efficiently from β-ionone by replacement of the metalating reagent from pentacarbonyliron(0) (20%) to dodecacarbonyltriiron(0)[14] (98%). Treatment of **7** with the lithium salt of acetonitrile in THF at −70 °C afforded **8** in 91% yield *via* addition, dehydration, and successive migration of tricarbonyliron (Scheme 2). A similar migration of tricarbonyliron has been already reported by Salzer *et al.* in the reaction of sorbaldehyde−tricarbonyliron with carbanions.[15] The geometry of the double bond at the 9 position of **8** was determined as *E* compared to the corresponding β-ionylideneacetonitrile **9**[16] after oxidative decomplexation using copper(II) chloride in ethanol.[17] The transformation of **8** to the corresponding aldehyde **10** was achieved quantitatively by DIBALH reduction. Decomplexation of **10** by copper(II) chloride in ethanol gave a complex mixture, and the desired product **2a** was not obtained. When decomplexation of **10** was carried out by using iron(III) chloride,[17] isomerization occurred to provide an isomeric mixture of double bonds at the 9

Scheme 2



Scheme 3



position. Therefore, the uncomplexed 7*E*,9*E*-aldehyde **2a** was prepared from **9** by DIBALH reduction in quantitative yield without isomerization of the double bond.

Next, we focused our attention on the stereoselective synthesis of 7*E*,9*Z*-aldehyde **2b**. Recently, Grëe and coworkers developed a convenient method for the isomerization of *E*,*E*-dienals to *E*,*Z*-dienals *via* an iron pentadienyl cation complex obtained from the corresponding dienol.[18] In order to apply this methodology to the synthesis of **2b**, the aldehyde−tricarbonyliron complex **10** was converted to the *E*,*E*-dienol **11** in excellent yield by $NaBH_4$ reduction (Scheme 3). Treatment of **11** with triphenylcarbenium tetrafluoroborate gave the dehydrated product **13** in 77% yield. None of the desired *Z*,*E*-dienol **14** was detected. The formation of **13** is easily understandable from consideration of the pentadienyl cation intermediate **12**, which is immediately deprotonated from the methylene group at the 4 position to afford **13**. The stereochemistry of **13** at the 6 and 8 positions was determined to be that shown in Scheme 3 by 2D NOESY experiments. Thus, the presence of corresponding crosspeaks confirms the proximity of H-7 (δ 5.71) to Me-5 (δ 1.83) and the proximityt of H-8 (δ 2.22) to Me-1 (δ 1.18 and 1.30) and H-11 (δ 0.40).

Subsequently, we studied the reaction of **7** with another nucleophile (Scheme 4). The reaction of **7** with the lithium enolate of ethyl acetate in THF at −70 °C gave the adduct **15** as a single product in 89% yield. In comparison with the reaction of acetonitrile, in this case dehydration and subsequent migration of the tricarbonyliron complex was not observed. We suppose that the

(11) (a) Dugger, R. W.; Heathcock, C. H. *Synth. Commun.* **1980**, *10*, 509. (b) Robeson, C. D.; Cawley, J. D.; Weisler, L.; Stern, M. H.; Eddinger, C. C.; Chechak, A. J. *J. Am. Chem. Soc.* **1955**, *77*, 4111. (c) Ishikawa, Y. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 1527. (d) Köbrich, von G.; Breckoff, W. E.; Drischel, W. *Liebigs Ann. Chem.* **1967**, *704*, 51. (e) Arens, J. F.; van Dorp, D. A. *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 973. (f) Pardoen, J. A.; Mulder, P. P. J.; van den Berg, E. M. M.; Lugtenburg, J. *Can. J. Chem.* **1985**, *63*, 1431.

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(13) Cais, M.; Maoz, N. *J. Organomet. Chem.* **1966**, *5*, 370.

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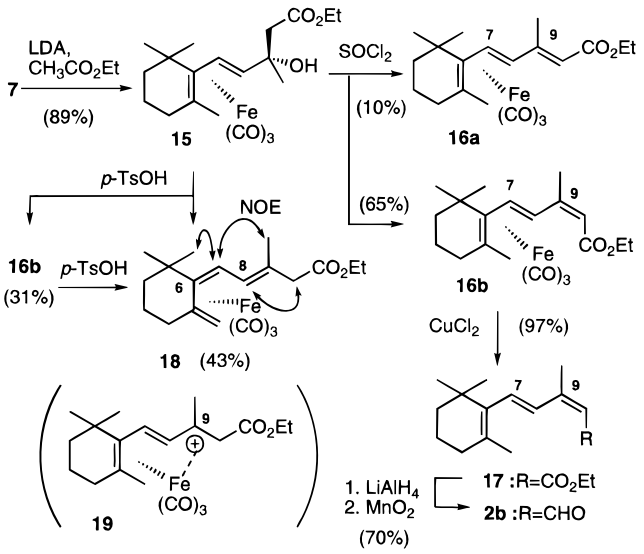
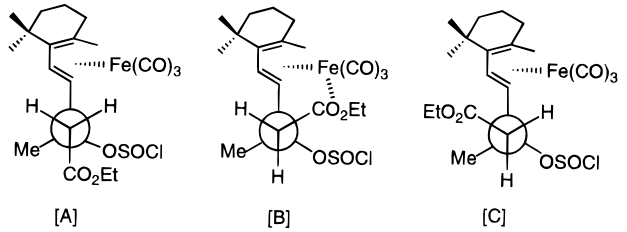
Scheme 4



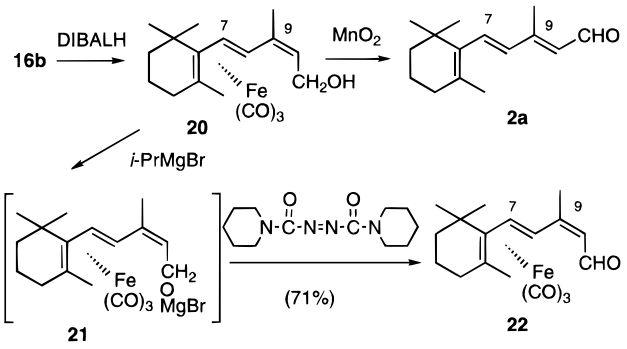
electron-withdrawing effect of the ester is less than that of the nitrile, so dehydration does not occur under the reaction conditions from the reaction intermediate. The structure of **15** was confirmed by single-crystal X-ray analysis.[19] Furthermore, this structure was consistent with the deduction from the reaction mechanism that the carbonyl group of **7** has the s-*cis* conformation and the nucleophile attacks the other side of the tricarbonyliron complex.[20] Dehydration of **15** by thionyl chloride afforded the 9*Z*-ester **16b** predominantly (65%) accompanied by its 9*E*-isomer **16a** (10%). The stereochemistry of the newly produced double bond of these compounds was determined by their transformation to the corresponding β-ionylidene esters[11b] (**17** and its isomer) after oxidative decomplexation. In contrast, treatment of **15** with *p*-TsOH under reflux in benzene afforded the 9*Z*-ester **16b** (31%) and the nonconjugated ester **18**[13] (43%). It is noteworthy that **16b** was isomerized to **18** under the reaction conditions, and this fact indicates that ester **18** seems to be the thermodynamically more stable product. The formation of **18** was rationalized from consideration of the transoid pentadienyl cation intermediate[21] **19**, which was immediately deprotonated from the five methyl group in the same manner as **13** to provide **18**. This reaction mechanism predicts that the stereochemistry of **18** at the 6 and 8 positions are *Z* and *E*, respectively, because elimination of the hydroxyl group occurs from the back side of the tricarbonyliron complex and spontanious deprotonation gives the product **18**. This speculation is in accordance with the confirmed structure determined by 2D NOESY experiments. Thus, the presence of corresponding crosspeaks confirms the proximity of H-7 (δ 3.14) to Me-1 (δ 1.20 and 1.24) and Me-9 (δ 1.75) and the proximity of H-8 (δ 5.02) to CH_2-9 (δ 2.83 and 2.88).

It is well-known that dehydration with thionyl chloride proceeds *via* an E_1 mechanism to afford the most stable product.[22] However, in the case of **15**, the unstable

Scheme 5



Scheme 6



Z-olefin **16b** was obtained as the major product. The high stereoselectivity of this dehydration can be understood by a chelation mechanism between the iron and the ester group in the reaction intermediate as shown in the Newman projections (Scheme 5). In the favored transition state [B], the tricarbonyliron group plays an important role in regulating the formation of the double bond. There are two possible routes for the formation of the *Z*-olefin through the transition state [B]: (i) *syn*-elimination *via* a six-membered cyclic intermediate as in the pyrolysis of esters, thioesters, and carbamates[23] (route A) or (ii) *anti*-elimination through a carbonium cation intermediate derived from the E_1 mechanism (route B). Although we could not obtain definite evidence, route B seems most likely for the formation of the *Z*-olefin because of the fact that dehydration by *p*-TsOH, in which reaction route A is impossible, gave the *Z*-olefin **16b** in 31% yield. A similar chelation mechanism between iron and a carbonyl group has already been reported in the hydroxylation of a phenoxo ferric complex to a catecholate complex with *m*-chloroperoxybenzoic acid.[24] In addition, the significance of chelation between the iron and the ester is supported by the results that in the dehydration of the adduct prepared from the reaction of **7** with a nucleophile not having a heteroatom such as ethylmagnesium bromide or vinylmagnesium bromide, only a complex mixture was produced and the *Z*-olefin was not isolated at all.

Our first attempt at transformation of **16b** to the aldehyde **2b** by DIBALH reduction and subsequent MnO_2 oxidation of the alcohol **20** following decomplexation was unsuccessful because isomerization of the double bond gave the 7*E*,9*E*-aldehyde **2a** (Scheme 6). It seems that the aldehyde is not a suitable functional group in the decomplexation step; the reason is not clear yet. There-

(19) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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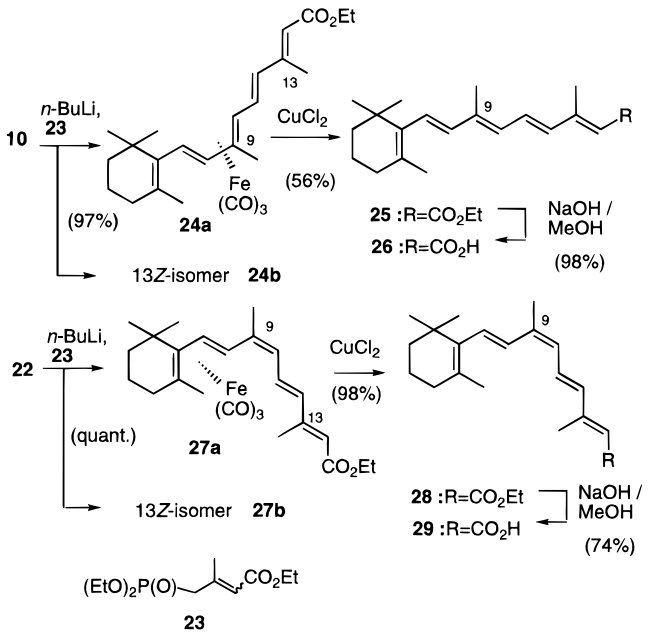
Scheme 7



fore, after decomplexation of **16b**, the ester **17** was converted to the aldehyde **2b** by $LiAlH_4$ reduction and subsequent MnO_2 oxidation. It is the first time that a stereoselective synthesis of **2b** has been achieved using a tricarbonyliron complex (Scheme 6). Alternatively, alcohol **20** was converted to the aldehyde **22** in good yield without decomplexation by mild oxidation using Mukaiyama's method.[25]

Finally, the aldehydes **10** and **22** were converted to the corresponding retinoic acids (Scheme 7). The Emmons−Horner reaction of **10** with the C5-phosphonate **23** was carried out using *n*-BuLi to give the ester **24a** and its 13*Z* isomer **24b**. The stereochemistry (*E*-form) of the 11,12 double bond in **24a**,**b** was determined on the basis of the coupling constants of the 11-H signal in the NMR spectrum. It is noteworthy that although the C5-phosphonate **23** was used as a mixture of double bonds [*ca.* 4:1] in the condensation, the ratio of the all-*E*-isomer in the products increased dramatically [all-*E*:13*Z* = *ca.* 12:1]. A similar result has been reported by Gedye and coworkers.[26] After decomplexation of **24**, the final transformation of **25** to the corresponding acid **26**[27] was achieved by hydrolysis using sodium hydroxide at 50 °C in 98% yield. In the same manner, the aldehyde **22** was converted to the corresponding (9*Z*)-retinoic acid **29**[28] in good yield.

In summary, we have developed a stereoselective synthesis of **2** which, for the first time, includes a *Z*-trisubstituted olefin in the polyene chain. This method will provide a novel route for the preparation of (*all-E*)- or (9*Z*)-vitamin A and related compounds.

Experimental Section

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. Analytical HPLC was carried out with a column, LiChrosorb Si-60 (5 μm), 0.4 × 30 cm, and preparative HPLC with a LiChrosorb Si-60 (5 μm), 1.0 × 30 cm. Column chromatography (CC) under reduced pressure by aspirator (*ca.* 30 mmHg) was performed by using Merck silica gel 60. All reactions were carried out under a nitrogen atmosphere. Materials were obtained from commercial supplies and used without further purification except when otherwise noted. THF and ether were purified by distillation from benzophenone−sodium ketyl under nitrogen. Diisopropylamine was purified by distillation from CaH_2. 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[(η^4-3,4,1,2)-(3*E*)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one]iron(0) (7). A mixture of β-ionone (2.85 g, 15 mmol) and dodecacarbonyltriiron[14] (9 g, 29 mmol) in benzene (40 mL) was heated under reflux for 20 h. The resulting mixture was passed through out the short aluminum column to remove the excess reagent, and eluent was concentrated under reduced pressure. The residue was purified by CC (ether:hexane 1:6) to give the tricarbonyliron complex **7**[13] (4.9 g, 98%) as orange solids: UV−vis 252.5 nm (sh); IR 2050, 1980 and 1960 ($Fe(CO)_3$), 1670 (ketone) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.22 (s, 3H), 1.41 (s, 3H), 1.45 (s, 3H), 1.5−1.7 (m, 4H), 1.8−2.1 (m, 2H), 2.17 (s, 3H), 2.40 (d, J = 9 Hz, 1H), 5.66 (d, J = 9 Hz, 1H); ^{13}C NMR (75 MHz) δ 19.6, 24.1, 29.7, 29.9, 34.1, 35.3, 38.7, 42.4, 51.6, 70.3, 81.5, 117.2, 204.6 (4C).

Tricarbonyl[(η^4-2,3,4,5)-(2*E*,4*E*)-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienenitrile]iron-(0) (8). To a stirred solution of LDA, prepared from *n*-BuLi (1.6 M hexane solution, 5.7 mL, 9.1 mmol) and diisopropylamine (1.3 ml, 9.1 mmol) in THF (30 mL), was added a solution of acetonitrile (0.52 mL, 9.1 mmol) in THF (6 mL) at −70 °C, and the resulting mixture was stirred for an additional 30 min. A solution of the tricarbonyliron complex **7** (1.0 g, 3.01 mmol) in THF (10 mL) was added at −70 °C, and the mixture was allowed to come to −50 °C. After addition of saturated aqueous NH_4Cl (40 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 nitrile **8** (967 mg, 91%) as orange prisms: mp 110−113 °C (ether−hexane); UV−vis 327, 243 nm; IR 2200 (nitrile), 2050 and 2000 ($Fe(CO)_3$) cm^{-1}; ^{1}H NMR (200 MHz) δ 0.48 (s, 1H), 1.13 (s, 3H), 1.24 (s, 3H), 1.4−1.6 (m, 4H), 1.83 (s, 3H), 1.95 (d, J = 11 Hz, 1H), 2.02 (br t, J = 6 Hz, 2H), 2.51 (s, 3H), 5.89 (d, J = 11 Hz, 1H); ^{13}C NMR (75 MHz) δ 18.7, 21.0, 23.1, 25.4, 28.9, 29.6, 34.8, 35.2, 42.1, 65.1, 87.6, 95.9, 120.8, 134.4, 137.3, 209.6 (3C); HRMS calcd for $C_{18}H_{21}FeNO_3$ 355.0872, found 355.0866 (M^+).

(2*E*,4*E*)-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienenitrile (9). To a stirred solution of nitrile **8** (350 mg, 0.99 mmol) in ethanol (20 mL) was added a solution of copper(II) chloride (570 mg, 4.2 mmol) in ethanol (10 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 3:7) to give the decomplexed nitrile **9**[16] (202 mg, 95%) as a pale yellow oil: UV−vis 304, 252 nm; IR 2200 (nitrile), 1680 and 1605 (double bond) cm^{-1}; ^{1}H NMR (200 MHz) δ 1.02 (s, 6H), 1.4−1.7 (m, 6H), 1.70 (s, 3H), 2.04 (br t, 2H), 2.20 (s, 3H), 5.16 (s, 1H), 6.14 (d, J = 16.5 Hz, 1H), 6.59 (d, J = 16.5 Hz, 1H).

Tricarbonyl[(η^4-2,3,4,5)-(2*E*,4*E*)-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal]iron(0) (10). To a solution of nitrile **8** (300 mg, 0.85 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise DIBALH (0.20 mL, 1.10 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 DIBALH 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 **10** (204 mg, quantitative) as orange prisms: mp 78.5−80 °C (ether−hexane); UV−vis 261 (sh) nm; IR 2049 and 1980 ($Fe(CO)_3$),

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1680 (aldehyde), 1650 (double bond) cm^{-1}; ^1H NMR (200 MHz) δ 1.08 (d, J = 6.5 Hz, 1H), 1.08 and 1.27 (each s, each 3H), 1.4−1.6 (m, 4H), 1.84 (s, 3H), 2.04 (br t, J = 7 Hz, 2H), 2.42 (d, J = 11 Hz, 1H), 2.58 (s, 3H), 5.89 (d, J = 11 Hz, 1H), 9.49 (d, J = 6.5 Hz, 1H); ^{13}C NMR (75 MHz) δ 19.3, 20.5, 23.7, 29.4, 30.3, 35.5, 35.8, 42.6, 56.9, 66.2, 89.3, 98.6, 135.2, 137.7, 195.8, 210.8 (3C); HRMS calcd for $C_{18}H_{21}FeO_4$ 358.0868, found 358.0868 (M^+).

(2*E*,4*E*)-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal (2a). In the same manner as described for the preparation of **10** from **8**, the nitrile **9** (185 mg, 0.86 mmol) was converted to the corresponding aldehyde **2a** (188 mg, quant.). The IR and ^1H NMR spectra are consistent with those of literature.[11a]

Tricarbonyl[(η^4-2,3,4,5)-(2*E*,4*E*)-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienol]iron(0) (11). To a stirred solution of the aldehyde **10** (700 mg, 2.0 mmol) in ethanol (7 mL) was added $NaBH_4$ (148 mg, 3.9 mmol) portionwise at 0 °C, and the mixture was stirred for an additional 30 min. The reaction mixture was poured into ice−water (15 mL), and the organics were extracted with ether followed by standard workup. The residue was purified by CC (ether: hexane 3:7) to provide the alcohol−iron complex **11** (543 mg, 76%) as a pale yellow oil: UV−vis 317.5 (sh), 205 nm; IR 3613 and 3500−3200 (hydroxy), 2050, 1980 and 1960 ($Fe(CO)_3$) cm^{-1}; ^1H NMR (300 MHz) δ 1.01 (br t, J = 6.5 Hz, 1H), 1.14 and 1.24 (each s, each 3H), 1.3−1.6 (m, 4H), 1.79 (s, 3H), 1.82 (d, J = 11 Hz, 1H), 1.9−2.1 (m, 2H), 2.30 (s, 3H), 3.81 (dd, J = 2, 8 Hz, 1H), 3.90 (dd, J = 12, 6 Hz, 1H), 5.70 (d, J = 11 Hz, 1H); HRMS calcd for $C_{18}H_{22}FeO_3$ 342.0919, found 342.0922 ($M^+ - H_2O$).

Tricarbonyl[(η^4-1,2,3,4)-(3*Z*,5*Z*)-3-methyl-5-(2,6,6-trimethyl-2-cyclohexenylidene)-1,3-pentadiene]iron(0) (13). To a stirred solution of the alcohol complex **11** (211 mg, 0.59 mmol) in CH_2Cl_2 (10 mL) was added a solution of triphenylcarbenium tetrafluoroborate (193 mg, 0.59 mmol) in CH_2Cl_2 (3 mL) at 0 °C, and the resulting mixture was stirred for an additional 15 min. After addition of water (15 ml), the mixture was stirred for 30 min and the organics were extracted with CH_2Cl_2 followed by standard workup. The residue was purified by CC (ether:hexane 5:95) to give the triene complex **13** (153 mg, 77%) as a pale yellow oil: UV−vis 324 (sh), 281 nm; IR 2050, 1980 and 1960 ($Fe(CO)_3$) cm^{-1}; ^1H NMR (200 MHz) δ 0.40 (dd, J = 9, 3 Hz, 1H), 1.18 and 1.30 (each s, each 3H), 1.49 (t, J = 6.5 Hz, 2H), 1.70 (dd, J = 7, 3 Hz, 1H), 1.83 (br s, 3H), 2.0−2.1 (m, 2H), 2.22 (d, J = 12 Hz, 1H), 2.27 (s, 3H), 5.18 (br t, J = 8 Hz, 1H), 5.71 (d, J = 12 Hz, 1H), 5.73 (br t, J = 4.5 Hz, 1H); ^{13}C NMR (75 MHz) δ 20.7, 23.2, 24.6, 29.3, 30.7, 36.5, 37.7, 41.7, 65.5, 84.3, 101.4, 125.6, 129.1, 135.6, 145.5, 213.6 (3C); HRMS calcd for $C_{18}H_{22}FeO_3$ 342.0919, found 342.0910 (M^+).

Tricarbonyl[ethyl (η^4-4,5,1,2)-(4*E*)-(3*R,4*R**,2*S**)-3-hydroxy-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-4-pentenoate]iron(0) (15).** In the same manner as described for the preparation of **8**, the tricarbonyliron complex **7** (1.0 g, 3.1 mmol) was reacted with ethyl acetate (0.61 mL, 6.2 mmol). The residue was purified by CC (ether:hexane 1:4) to give the adduct complex **15** (1.16 g, 89%) as pale yellow prisms: mp 85−86 °C (CH_2Cl_2−hexane); UV−vis 237 nm (sh); IR 3500 (hydroxy), 2050, 1980 and 1960 ($Fe(CO)_3$) cm^{-1}; ^1H NMR (200 MHz) δ 1.07 (s, 3H), 1.28 (t, J = 7 Hz, 3H) 1.37 and 1.40 (each s, each 3H), 1.42 (s, 3H), 1.4−1.6 (m, 4H), 1.7−2.0 (m, 2H), 2.12 (d, J = 9 Hz, 1H), 2.63 (s, 2H), 3.67 (s, 1H), 4.21 (q, J = 7 Hz, 2H), 5.17 (d, J = 9 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.2, 19.6, 23.4, 30.0, 30.9, 34.2, 34.9, 39.1, 42.6, 48.8, 60.9, 67.0, 69.1, 71.4, 79.6, 112.3, 172.4, 210.5 (3C); HRMS calcd for $C_{20}H_{27}FeO_5$ 403.1207, found 403.1220 ($M^+ - OH$).

Tricarbonyl[ethyl (η^4-4,5,1,2)-(2*E*,4*E*)-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienoate]iron(0) (16a) and Tricarbonyl[ethyl (η^4-4,5,1,2)-(2*Z*,4*E*)-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienoate]-iron(0) (16b). To a solution of the hydroxy ester **15** (200 mg, 0.48 mmol) in pyridine (2 mL) was added thionyl chloride (0.06 mL, 0.96 mmol) at 0 °C, and the resulting mixture was stirred for 10 min. The reaction was quenched with 5% HCl (10 mL) in the ice−bath, and the organics were extracted with ether followed by standard workup. The residue was purified by CC (ether:hexane 1:9) to give the esters **16a** (20 mg, 10%) and **16b** (124 mg, 65%) as pale orange solids, respectively.

16a: UV−vis 280 (sh) nm; IR 2050 and 1980 ($Fe(CO)_3$), 1688 (ester), 1603 (double bond) cm^{-1}; ^1H NMR (200 MHz) δ 1.28 (s, 3H), 1.30 (t, J = 7 Hz, 3H), 1.43 and 1.49 (each s, each 3H), 1.5−1.8 (m, 4H), 1.8−2.0 (m, 2H), 2.27 (s, 3H), 2.67 (d, J = 9 Hz, 1H), 4.18 (q, J = 7 Hz, 2H), 5.38 (d, J = 9 Hz, 1H), 5.79 (s, 1H); ^{13}C NMR (75 MHz) δ 14.4, 18.3, 19.6, 23.7, 29.7, 34.2, 35.2, 38.9, 42.6, 58.6, 59.6, 68.4, 79.3, 113.3, 114.6, 159.0, 166.7, CO disappeared; HRMS calcd for $C_{20}H_{26}FeO_5$ 402.1131, found 402.1121(M^+).

16b: UV−vis 285 (sh) nm; IR 2050 and 1970 ($Fe(CO)_3$), 1690 (ester), 1605 (double bond) cm^{-1}; ^1H NMR (200 MHz) δ 1.29 (t, J = 7 Hz, 3H) 1.36 (s, 3H), 1.41 and 1.46 (each s, each 3H), 1.5−1.7 (m, 4H), 1.82 (s, 3H) 1.8−2.0 (m, 2H), 4.20 (q, J = 7 Hz, 2H), 4.74 (d, J = 9.5 Hz, 1H), 5.38 (d, J = 9.5 Hz, 1H), 5.68 (s, 1H); ^{13}C NMR (75 MHz) δ 14.4, 19.6, 20.4, 23.5, 29.6, 34.3, 35.2, 42.7, 53.7, 59.6, 69.2, 82.0, 114.1, 115.7, 158.0, 166.3, 211.3 (3C); HRMS calcd for $C_{20}H_{26}FeO_5$ (M^+) 402.1131, found 402.1129.

Ethyl (2*Z*,4*E*)-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienoate (17). To a stirred solution of the ester complex **16b** (1.28 g, 3.18 mmol) in ethanol (50 mL) was added a solution of copper(II) chloride (2.14 g, 15.9 mmol) in ethanol (20 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 1:7) to give the decomplexed ester **17** (808 mg, 97%) as a pale yellow oil. The IR and ^1H NMR spectra are consistent with those of literature.[11b]

Tricarbonyl[ethyl (η^4-5,1,2,1)-(3*E*,5*Z*)-3-methyl-5-((6,6-dimethyl-2-methylidene)cyclohexylidene)-3-pentenoate]-iron(0) (18). A mixture of the ester complex **15** (664 mg, 1.58 mmol) and *p*-TsOH (25 mg) in benzene (30 mL) was heated under reflux for 0.5 h. After cooling, water (40 mL) was added and then the organics were extracted with benzene followed by standard workup. The residue was purified by CC (ether: hexane 1:7) to afford the esters **16b** (197 mg, 31%) and **18**[13] (271 mg, 43%) as pale yellow oils, respectively.

18: UV−vis 240 nm (sh); IR 2050, 1975 and 1960 sh ($Fe(CO)_3$), 1720 (ester) cm^{-1}; ^1H NMR (200 MHz) δ 1.20 (3H, s, 3H) 1.23 (t, J = 7 Hz, 3H) 1.24 (s, 3H), 1.6−1.7 (m, 2H), 1.69 (d, J = 2 Hz, 1H), 1.72 (d, J = 2 Hz, 1H), 1.75 (s, 3H), 1.8−1.9 (m, 2H), 2.08 (dt, J = 16.5, 5 Hz, 1H), 2.75 (1H, ddd, J = 16.5, 8, 6 Hz, 1H), 2.83 (d J = 14.5 Hz, 1H), 2.88 (1H, d, J = 14.5 Hz, 1H), 3.14 (d, J = 8.5 Hz, 1H), 4.10 (q, J = 7 Hz, 2H), 5.02 (d, J = 8.5 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.2, 17.3, 18.9, 30.5, 32.9, 33.3, 33.9, 37.6, 39.3, 44.9, 45.4, 60.5, 107.0, 113.3, 129.8, 130.6, 171.4, 211.0 (3C); HRMS calcd for $C_{20}H_{26}FeO_5$ (M^+) 402.1131, found 402.1120 (M^+).

(2*Z*,4*E*)-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal (2b). A solution of the ester **17** (83 mg, 0.32 mmol) in ether (4 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (24 mg, 0.63 mmol) in ether (4 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 30 min. The excess $LiAlH_4$ was destroyed by addition of moist ether and water, and then the organics were extracted with ether followed by standard workup. To the residue were added active MnO_2 (560 mg, 6.4 mmol) and CH_2Cl_2 (15 mL), and the resulting mixture was shaken at rt for 5 h. The mixture was filtered through Celite, and the filtrate was concentrated *in vacuo* to give the crude product, which was purified by CC (ether:hexane 1:7) to afford the aldehyde **2b** (180 mg, 79%) as a yellow oil. The IR and ^1H NMR are consisted with those of literature.[11b]

Tricarbonyl[(η^4-4,5,1,2)-(2*Z*,4*E*)-3-methyl-5-(2,6,6-trimethyl-1-cycohexen-1-yl)-2,4-pentadienal]iron(0) (22). To a solution of the ester complex **16b** (700 mg, 1.74 mmol) in dry ether (10 mL) was added dropwise DIBALH (0.7 mL, 4 mmol) in dry ether (3 mL) at −45 °C. After the solution was stirred at the same temperature for an additional 30 min, the excess DIBALH was destroyed by addition of moist ether and water. Cold 15% tartaric acid (4.5 mL, 4.5 mmol) was added, and the resulting mixture was stirred at rt for 2 h. The

organics were extracted with ether followed by standard workup. To a dissolved solution of this residue in dry THF (10 mL) was added diisopropylmagnesium bromide (0.68 M ether solution, 3.3 mL, 2.26 mmol) at 0 °C. After the solution was stirred for 10 min, a solution of azodicarbonyldipiperidine (530 mg, 1.24 mmol) in dry THF (4 mL) was added at 0 °C, and the resulting mixture was stirred for an additional 20 min. The reaction was quenched with brine (20 mL), and then the organics were extracted with ether (3 × 30 mL) followed by standard workup. The residue was purified by CC (ether: hexane 1:4) to afford the aldehyde complex **22** (445 mg, 71%) as a yellow oil: UV−vis 301.8 nm; IR 2038, 1978 and 1960 sh ($Fe(CO)_3$), 1655 (aldehyde) cm^{-1}; ^1H NMR (300 MHz) δ 1.33 (3H, s, 3H), 1.42 and 1.47 (each s, each 3H), 1.5−1.7 (m, 4H), 1.8−2.1 (m, 2H), 1.97 (s, 3H), 4.05 (d, J = 10 Hz, 1H), 5.46 (d, J = 10 Hz, 1H), 5.86 (d, J = 6 Hz, 1H), 10.07 (d, J = 6 Hz, 1H); ^{13}C NMR (75 MHz) δ 19.3, 23.7, 25.7, 29.5, 30.4, 35.6, 36.1, 42.6, 58.9, 69.0, 95.3, 100.0, 135.8, 137.4, 194.5, 210.5 (3C); HRMS calcd for $C_{18}H_{22}FeO_4$ 358.0868, found 358.0868 (M^+).

Tricarbonyl[ethyl (η^4-7,8,9,10)-(*all-E*)-retinoate]iron-(0) (24a) and Tricarbonyl[ethyl (η^4-7,8,9,10)-(13*Z*)-retinoate]iron(0) (24b). To a solution of diethyl (3-(methoxycarbonyl)-2-methyl-2-propenyl)phosphonate (**23**)[26] (*E*:*Z* = 4:1) (391 mg, 2 mmol) in THF (5.5 mL) was added *n*-BuLi (1.6 M hexane solution, 0.99 mL, 1.66 mmol) at 0 °C. After the mixture was stirred for 30 min, a solution of the aldehyde complex **10** (280 mg, 0.78 mmol) in THF (5 mL) was added. The resulting mixture was stirred for an additional 5 h. The reaction was quenched with saturated NH_4Cl (5 mL) and extracted with ether followed by standard workup. The residue was purified by CC (ether:hexane 1:9) to give the pentaenyl ester **24a** (328 mg, 89%) and its isomer **24b** (27 mg, 7%) as yellow oils, respectively.

***all-E*-Isomer 24a:** UV−vis 318.4 nm; IR 2035 and 1972 ($Fe(CO)_3$), 1700 (ester), 1606 (double bond) cm^{-1}; ^1H NMR (300 MHz) δ 1.15 and 1.27 (each s, each 3H), 1.28 (t, J = 7 Hz, 3H), 1.4−1.6 (m, 4H), 1.73 (d, J = 9 Hz, 1H), 1.82 (s, 3H), 2.01 (br t, J = 7.5 Hz, 2H), 2.05 (d, J = 11 Hz, 1H), 2.28 (s, 3H), 2.38 (s, 3H), 4.17 (q, J = 7 Hz, 2H), 5.70 (d, J = 11 Hz, 1H), 5.77 (s, 1H), 6.31 (d, J = 15 Hz, 1H), 6.38 (dd, J = 15, 9 Hz, 1H); ^{13}C NMR (75 MHz) δ 13.8, 14.4, 18.9, 20.1, 23.0, 28.9, 29.8, 34.9, 35.2, 42.2, 59.7, 60.6, 61.7, 85.5, 95.5, 118.5, 133.6, 134.5, 134.9, 135.1, 152.0, 167.2, 212.5 (3C); HRMS calcd for $C_{25}H_{32}FeO_5$ 468.1600, found 468.1592 (M^+).

13*Z*-Isomer 24b: UV−vis 329.2nm; IR 2034 and 1973 ($Fe(CO)_3$), 1702 (ester), 1610 (double bond) cm^{-1}; ^1H NMR (300 MHz) δ 1.15 and 1.27 (each s, each 3H), 1.28 (t, J = 7 Hz, 3H), 1.4−1.6 (m, 4H), 1.82 (s, 3H), 1.85 (d, J = 10.5 Hz, 1H), 2.00 (s, 1H), 2.01 (br t, J = 7.5 Hz, 2H), 2.08 (d, J = 10.5 Hz, 1H), 2.37 (s, 3H), 4.16 (q, J = 7 Hz, 2H), 5.65 (s, 1H), 5.70 (d, J = 10.5 Hz, 1H), 6.32 (dd, J = 15.5, 10.5 Hz, 1H), 7.85 (dd, J = 15.5 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.3, 18.9, 20.2, 20.9, 23.1, 28.9, 29.9, 34.9, 35.2, 42.2, 59.7, 61.0, 61.9, 85.7, 96.0, 116.3, 127.7, 134.9, 135.1, 136.2, 150.6, 166.5, 212.5 (3C); HRMS calcd for $C_{25}H_{32}FeO_5$ 468.1600, found 468.1600 (M^+).

Ethyl (*all-E*)-Retinoate (25). In the same manner as described for the decomplexation of **8**, the retinoate complex **24a** (66 mg, 0.14 mmol) was converted to the corresponding retinoate **25** (26 mg, 56%). The IR and ^1H NMR spectra are consistent with those of literature.[27]

(*all-E*)-Retinoic Acid (26). A mixture of the retinoate **25** (25 mg, 0.78 mmol) and 25% NaOH solution (5 mL) in methanol (5 mL) was heated at 50 °C for 30 min. After cooling, the reaction mixture was made acidic with 5% HCl, and then the organics were extracted with ethyl acetate followed by standard workup. The residue was purified by CC (ethyl acetate:hexane 3:1) to give the retinoic acid **26** (23 mg, 98%) as yellow solids. The IR and ^1H NMR spectra are consistent with those of literature.[27]

Tricarbonyl[ethyl (η^4-5,6,7,8)-(9*Z*)-retinoate]iron(0) (27a) and Tricarbonyl[ethyl (η^4-5,6,7,8)-(9*Z*,13*Z*)-retinoate]-iron(0) (27b). In the same manner as described for the preparation of **24**, the aldehyde complex **22** (33 mg, 0.09 mmol) was converted to the corresponding retinoate−tricarbonyliron complex **27** as a isomeric mixture (54 mg, quant). Pure samples were obtained by HPLC (ether:benzene:hexane 1:25: 74) separation as pale yellow oils, respectively.

9*Z*-Isomer 27a: UV−vis 365, 325 (sh), 260 nm; IR 2030, 1967 and 1950 ($Fe(CO)_3$), 1700 (ester), 1593 (double bond) cm^{-1}; ^1H NMR (300 MHz) δ 1.29 (s, 3H), 1.29 (t, J = 7 Hz, 3H), 1.42 and 1.47 (each s, each 3H), 1.5−1.7 (m, 4H), 1.87 (s, 3H), 1.9−2.0 (m, 2H), 2.36 (s, 3H), 3.45 (d, J = 10 Hz, 1H), 4.17 (q, J = 7 Hz, 2H), 5.25 (d, J = 10 Hz, 1H), 5.79 (s, 1H), 6.02 (d, J = 11.5 Hz, 1H), 6.23, (d, J = 15 Hz, 1H), 7.08 (dd, J = 15, 11 Hz, 1H); ^{13}C NMR (75 MHz) δ 13.5, 14.4, 19.6, 20.3, 23.3, 29.7, 34.2, 35.2, 39.0, 42.7, 55.4, 59.7, 67.5, 80.3, 113.6, 119.0, 127.9, 134.6, 142.0, 152.8, 167.2, 212.3 (3C); HRMS calcd for $C_{25}H_{32}FeO_5$ 468.1600, found 468.1581 (M^+).

9*Z*,13*Z*-Isomer 27b: UV−vis 360.4, 340 (sh), 261 nm; IR 2029 and 1965 ($Fe(CO)_3$), 1697 (ester), 1594 (double bond) cm^{-1}; ^1H NMR (300 MHz) δ 1.27 (s, 3H), 1.29 (t, J = 7 Hz, 3H), 1.42 and 1.46 (each s, each 3H), 1.5−1.7 (m, 4H), 1.87 (s, 3H), 1.8−2.0 (m, 2H), 2.08 (s, 3H), 3.47 (d, J = 9 Hz, 1H), 4.16 (q, J = 7 Hz, 2H), 5.25 (d, J = 9 Hz, 1H), 5.68 (s, 1H), 6.12 (d, J = 11.5 Hz, 1H), 7.08 (dd, J = 15, 11.5Hz, 1H), 7.73 (d, J = 15 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.4, 19.6, 20.3, 20.8, 23.3, 29.7, 34.2, 35.2, 39.0, 42.7, 55.6, 59.6, 67.2, 80.4, 113.3, 116.9, 128.7, 128.8, 130.9, 142.2, 151.3, 166.5, 212.5 (3C); HRMS calcd for $C_{25}H_{32}FeO_5$ 468.1600, found 468.1609 (M^+).

Ethyl (9*Z*)-Retinoate (28). In the same manner as described for the decomplexation of **8**, the retinoate complex **27a** (15 mg, 0.03 mmol) was converted to the corresponding retinoate **28** (10.3 mg, 98%). The IR and ^1H NMR spectra are consistent with those of literature.[28]

(9*Z*)-Retinoic Acid (29). In the same manner as described for the preparation of **26**, the retinoate **28** (50 mg, 0.15 mmol) was hydrolyzed to the corresponding retinoic acid **29** (37 mg, 74%) as yellow solids. The IR and ^1H NMR spectra are consistent with those of literature.[28]

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

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for compounds **7**, **8**, **10**, **13**, **15**, **16a**,**b**, **18**, **22**, **24a**,**b**, and **27a**,**b**, 2D-NOESY spectra for **13** and **18**, and an ORTEP diagram of the X-ray structure of adduct **15** (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961041+