Reactivity of Tricarbonyl(pentadienyl)iron(1+) Cations: Enantioselective Synthesis of 5-HETE Methyl Ester†

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The syntheses of racemic 5-HETE methyl ester (1) and of 5-HETE lactone (5-HL) were accomplished in 11 steps from tricarbonyl [1-(methoxycarbonyl)pentadienyl]iron(1+) hexafluorophosphate (2). A second synthesis of 1 from 2 in five steps was also achieved. Starting with optically active 5 the synthesis of (+)-1 and (−)-1 in high optical purity was realized. The stereochemistry of the 6,8-diene portion and the stereochemistry of the C5 asymmetric center of 1 were controlled by the (tricarbonyl)-iron adjunct.

Introduction

Oxidation of aracadonic acid by 5-lipoxygenase affords 5-hydroperoxyeicosatetraenoic acid (5-HPETE) from which the central leukotriene LTA_4 is formed by the enzyme dehydrase.[1] Subsequent metabolism of LTA_4 produces the dihydroxyeicosanoid LTB_4 and the peptidoleukotrienes LTC_4, LTD_4, and LTE_4. In addition, metabolism of 5-HPETE by the enzyme reductase affords 5-hydroxyeicosatetraenoic acid (5-HETE). The HETEs apparently do not act through specific receptors, but may play a biological role through incorporation into the lipids of cell membranes. Studies indicate that 5-HETE is incorporated into the microsomal and/or plasma membrane of MDCK cells and that 5-HETE decreases the ability of these cells to produce PGE_2. For this reason 5-HETE may have the ability to regulate renal function if released in proximity of the tubular epithelium during an inflammatory reaction.[2] Recently, it was found that 5-HETE and 5-HETE lactone (5-HL) were produced by human B cells which were incubated with the Ca^{2+} ionophore A23187. For this reason it was speculated that 5-HETE and 5-HL may play a role in B cell activation, since increased Ca^{2+} occurs during cross-linking of membrane Ig.[3]

While the leukotrienes represent a formidable synthetic challenge, nearly all of the members of this group have been successfully prepared.[4] The 5-HETE methyl ester (1) has been prepared in racemic[5] and optically active[6] form. We report herein a tactically novel synthesis of (±)-, (+)-, and (−)-1 and of (±)-5-HL.[7]

Results and Discussion

The stategy for the synthesis of 1, which relies upon a single adjunct to control both the stereochemistry of the 6*E*,8*Z*-diene and of the 5-hydroxyl functionality, is diagrammed in Scheme I.[8] The stereochemistry of the 6,8-diene portion will be established by nucleophilic addition to a (pentadienyl)$Fe(CO)_3$ cation (2).[9] The $Fe(CO)_3$ will then serve as a protecting and directing group for the formation of the C5 chiral center via a diastereoselective C–C bond formation.[10] The first goal is the preparation of the key tetraenal complex 3.

Preparation of (2(*E*),4(*Z*),7(*Z*),10(*Z*)-Hexadecatetraenal)$Fe(CO)_3$ (3). The known tricarbonyl(methyl 6-oxo-2,4-hexadienoate)iron (4) may be prepared by complexation of the free ligand[11] using $Fe_2(CO)_9$. The preparation of optically active 4 by resolution[12,13] has been reported. Using the method of Gree and Monpert[12b] (−)-4 was obtained in 82% of the theoretical yield. This compound was determined to be >88% ee by optical rotation and >94% ee by ^1H NMR analysis with the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-

† Taken in part from the Ph.D. Thesis of C.T., Marquette University, 1992.

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(2) Gordon, J. A.; Figard, P. H.; Quinby, G. E.; Spector, A. A. *Am. J. Physiol.* **1989**, *256*, C1–C10.

(3) Schulam, P. G.; Shearer, W. T. *J. Immunol.* **1990**, *144*, 2696–2701.

(4) For a good analysis of the synthetic challenges presented by the leukotrienes see: Rokach, J.; Guindon, Y.; Young, R. N.; Adams, J.; Atkinson, J. G. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons: New York, 1988; Vol. 7, p 141–273.

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(6) (a) Corey, E. J.; Hashimoto, S. *Tetrahedron Lett.* **1981**, *22*, 299–302. (b) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 999–1002. (c) Nicolaou, K. C.; Ladduwahetty, T.; Taffer, I. M.; Zipkin, R. E. *Synthesis* **1986**, 344–6. (d) Shimazaki, T.; Kobayashi, Y.; Sato, F. *Chem. Lett.* **1988**, 1785–8.

(7) Preliminary communication: Donaldson, W. A.; Tao, C. *Synlett* **1991**, 895–7.

(8) The use of the (tricarbonyl)iron adjunct for the synthesis of leukotrienes has also been examined by others: (a) Nunn, K.; Mosset, P.; Gree, R.; Saalfrank, R. W. *J. Org. Chem.* **1992**, *57*, 3359–64. (b) Franck-Neumann, M.; Colson, P.-J. *Synlett* **1991**, 891–4. (c) Gigou, A.; Beaucourt, J. P.; Lellouche, J. P.; Gree, R. *Tetrahedron Lett.* **1991**, *32*, 635–8. (d) Pinsard, P.; Lellouche, J. P.; Beaucourt, J. P.; Gree, R. *Tetrahedron Lett.* **1990**, *31*, 1141–4. (e) Gigou, A.; Lellouche, J. P.; Beaucourt, J. P.; Toupet, L.; Gree, R. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 755–7.

(9) (a) Donaldson, W. A.; Ramaswamy, M. *Tetrahedron Lett.* **1989**, *30*, 1339–42. (b) Yeh, M.-C. P.; Sun, M.-L.; Lin, S.-K. *Tetrahedron Lett.* **1991**, *32*, 113–6. (c) The reaction of 2 with alkynylcerium reagents occurs with poorer selectivity: Laabassi, M.; Gree, R. *Bull. Soc. Chim. Fr.* **1992**, *129*, 151–6.

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(11) Gree, R.; Tourbah, H.; Carrie, R. *Tetrahedron Lett.* **1986**, *27*, 4983–6.

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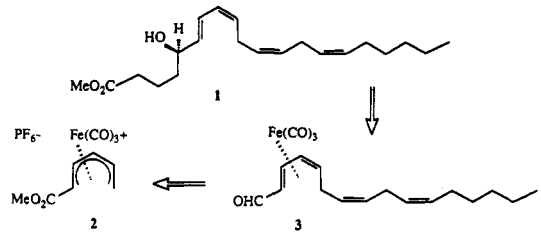
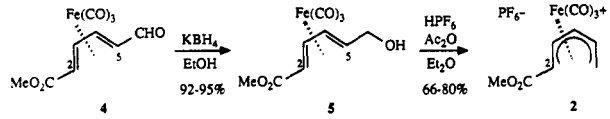
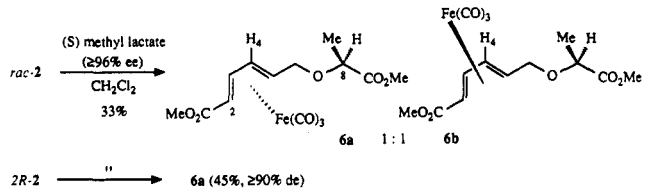
Scheme I



(+)-camphorato]europium(III) [Eu(tfc)$_3$].[14] Reduction of *rac*-**4** and of (−)-**4** by the literature procedure[15] gave the alcohols *rac*-**5** and (2*R*,5*S*)-**5** (92% and 95% respectively). Examination of *rac*-**5** by ^{1}H NMR spectroscopy in the presence of [Eu(tfc)$_3$] (1.9 equiv, d_6-acetone) indicated nearly base-line separation of the methoxycarbonyl signals (ca. 0.03 ppm difference). By this method, (2*R*,5*S*)-**5** was determined to be >92% ee.



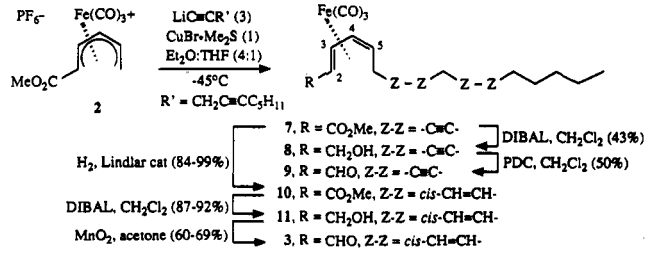
Treatment of *rac*-**5** and of (2*R*,5*S*)-**5** with HPF_6 gave the (1-(methoxycarbonyl)pentadienyl)iron(1+) cations *rac*-**2** and (1*R*)-**2** (66% and 80%, respectively). In CD_3NO_2 solution only the "U" or cisoid conformation[16] of the cation was observed, as determined by its characteristic ^{1}H NMR coupling constants.[17] The optical purity of the cation can not be directly assessed. Therefore, an indirect assessment of its optical purity was devised. Treatment of *rac*-**2** with (*S*)-methyl lactate in CH_2Cl_2 gave a 1:1 mixture of diastereomeric (2*E*,4*E*)-dienyl ethers **6a** and **6b** (33%). The 2*E*,4*E* assignments are based on a



comparison of the ^{1}H NMR spectra of **6a** and **6b** with the dienol complex **5**. Presumably these ethers arise via attack of methyl lactate on the "*S*" or transoid form of the pentadienyl cation.[18] The ^{1}H NMR spectra of the two diastereomers in C_6D_6 are quite different;[19] in particular, the signal for H4 of **6a** appears at δ 4.83 while the signal for H4 of **6b** appears at δ 4.71.[20] Reaction of (1*R*)-**2** with (*S*)-methyl lactate (>96% ee) gave **6a** (>90% de). *If it is assumed that no chiral recognition occurs during this reaction,*[21] *then* (2*R*)-**2** *is of* >86% *ee.*

We and others have shown that the reaction of 1-substituted (pentadienyl)iron(1+) cations with organocuprates occurs with high regioselectivity.[9] The reaction of the anion of 1,4-decadiyne with *rac*-**2** in the presence of CuBr·Me_2S gave a single isolable methyl diendiynoate complex *rac*-**7** (50–69%). In a similar fashion, (2*R*)-**2** gave (2*R*)-**7** (64%). The 2*E*,4*Z*-diene stereochemistry was assigned on the basis of its NMR spectral data. In particular, the signals for H3, H4, and H5 appear at δ 6.06 (ddd, J = 8.8, 5.4, 1.2), 5.32 (dd, J = 7.5, 5.4), and 2.89 (dq, J = 1.2, 7.7), respectively, while the signal for H2 appears overlapped with other signals at δ 2.10.[22] Additionally, the signals for C-3 and C-4 appear at δ 94.2 and 85.7 ppm, respectively. These chemical shifts are consistent with a 2*E*,4*Z*-dienoate complex.[9a,15] Examination of *rac*-**7** by ^{1}H NMR spectroscopy in the presence of [Eu(tfc)$_3$] (4.8 equiv, d_6-acetone) indicated base-line separation of the methoxycarbonyl signals (ca. 0.06 ppm difference). By this method, (2*R*)-**7** was determined to be >90% ee.

Reduction of *rac*-**7** with DIBAL in CH_2Cl_2 gave the corresponding dienediynol *rac*-**8** (43%) which was oxidized to the dienediynal *rac*-**9** (50%). It was found that the dienediyne complexes were highly unstable, as evidenced by a change in color from yellow to deep brown during storage under N_2 at 0 °C for 16 h. For this reason, the dienediynoates *rac*-**7** and (2*R*)-**7**, immediately following purification, were subjected to reduction with H_2 in the presence of Lindlar catalyst to afford the tetraenoates *rac*-**10** and (2*R*)-**10** (84–99% and 91%, respectively). The 2*E*,4*Z*-stereochemistry was assigned on the basis of its NMR spectral data. In particular, the signals for H2 and H3 appear at δ 2.23 (dd, J = 8.5, 1.0 Hz) and 6.07 (ddd, J = 8.7, 5.4, 1.0), while the signals for H4 and H5 appear overlapped with other signals at δ 5.35 and 2.72, respectively.[22] Additionally, the signals for C3 and C4 appear at δ 92.8 and 85.3 ppm, respectively. The 7*Z*,10*Z*-stereochemistry is assigned on the basis of the expected geometry for catalytic semihydrogenation of alkynes and was confirmed by eventual conversion of **10** to **1** (vide infra). Examination of *rac*-**10** by ^{1}H NMR spectroscopy in the presence of [Eu(tfc)$_3$] (5.5 equiv, d_6-acetone) indicated base-line separation of the methoxycarbonyl signals (ca. 0.08 ppm difference). By this method, (2*R*)-**10** was determined to be >90% ee.



Reduction of *rac*-**10** (DIBAL, CH_2Cl_2) gave *rac*-**11** (87–92%). The 2*E*,4*Z* diene stereochemical assignment was based on its NMR spectral data. In particular, the signal

(14) The assessment of the optical purity has previously been accomplished by use of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (Eu(hfc)$_3$]: Solladie-Cavallo, A.; Suffert, J. *Mag. Resn. Chem.* **1985**, *23*, 739–43. While these authors found good separation of the signals for the two enantiomers in $CDCl_3$ as solvent, we observed good signal separation only in d_6-acetone as solvent.

(15) Morey, J.; Gree, D.; Mosset, P.; Toupet, L.; Gree, R. *Tetrahedron Lett.* **1987**, *28*, 2959–62.

(16) Sorensen, T. S.; Jablonski, C. R. *J. Organomet. Chem.* **1970**, *25*, C62–C66.

(17) Donaldson, W. A.; Ramaswamy, M. *Synth. React. Inorg. Met.-Org. Chem.* **1987**, *17*, 49–56.

(18) The reaction of **2** in aqueous solution affords the 2*E*,4*Z*-dienol complex.[15]

(19) Notably, the ^{1}H NMR spectra of the two diastereomers were indistinguishable in $CDCl_3$ or d_6-acetone solution.

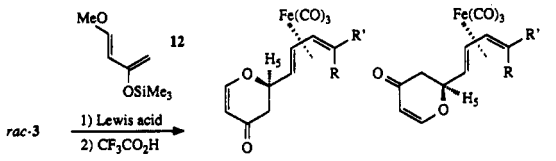
(20) The spectral assignments for **6a** (2*R*,5*S*,8*S*) and **6b** (2*S*,5*R*,8*S*) are based on the formation of **6a** from the reaction of (2*R*)-**2** with (*S*)-methyl lactate.

(21) It should be noted that examples of chiral recognition in the reaction of (diene)Fe(CO)$_3$ have been reported: Pinsard, P.; Lellouche, J. P.; Beaucourt, J. P.; Gree, R. *Tetrahedron Lett.* **1990**, *31*, 1137–40. Roush, W. R.; Park, J. C. *Tetrahedron Lett.* **1990**, *31*, 4707–10.

(22) Peak assignments were facilitated by 2D-COSY analysis.

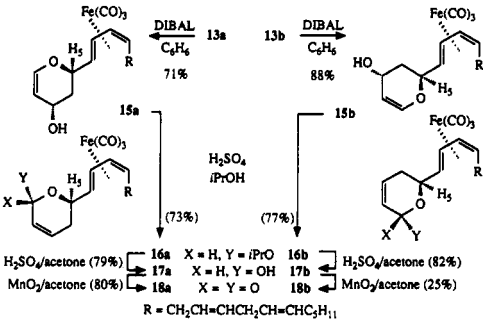
for H4 appears at δ 5.19 (dd, J = 7.3, 5.0 Hz) and the signals for C3 and C4 appear at δ 92.4 and 83.3 ppm, respectively. These chemical shifts and coupling constants are consistent with other known 2*E*,4*Z*-dienol complexes.[23] Oxidation of *rac*-**11** with pyridinium dichromate in the presence of 3A molecular sieves and acetic acid gave *rac*-**3** contaminated with about 20% of the free ligand, which was difficult to separate.[24] Oxidation of *rac*-**11** with a large excess of activated MnO_2 cleanly gave the desired tetraenal *rac*-**3** (60–69%). The 2*E*,4*Z* stereochemistry of **3** was assigned on the basis of its ^1H NMR spectral data. In particular, the signals for H2, H3, and H5 appear at δ 2.59 (ddd, J = 8.9, 3.8, 1.0 Hz), 6.05 (ddd, J = 8.7, 5.2, 1.2), and 2.89 (br q, J = 7.5 Hz) while the signal for H4 appears overlapped with other signals at δ 5.38.[22] Additionally, the signals for C3 and C4 appear at δ 91.1 and 86.6 ppm, respectively. Examination of *rac*-**11** and of *rac*-**3** by ^1H NMR spectroscopy in the presence of [Eu(tfc)$_3$] or [Pr(tfc)$_2$] using d_6-acetone, $CDCl_3$, C_6D_6, or CD_3CN as solvent failed to give satisfactory separation of the signals for the two enantiomers. For this reason, (2*R*)-**10** was transformed into (2*R*)-**3** by reduction (DIBAL, CH_2Cl_2) followed by oxidation (excess MnO_2) without isolation of the intermediate alcohol (65% overall). The optical purity of (2*R*)-**3** was not assessed. With the successful preparation of the key 2*E*,4*Z*,7*Z*,10*Z*-tetraenal complex **3** in racemic and optically active form, attention was next focused on introduction of the C1–C4 segment with establishment of the chiral center at C5.

Preparation of 5-HETE Methyl Ester by Hetero Diels–Alder Methodology. We have previously shown that the hetero Diels–Alder reaction of complexed dienals occurs in a diastereoselective fashion to afford a dienyldihydropyrone complex and that subsequent transformations of the dihydropyrone can afford a δ-lactone functionality.[10] This pathway was explored for the preparation of **1**. The reaction of *rac*-**3** with 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (**12**)[25] in the presence of a Lewis acid followed by workup with CF_3CO_2H gave a mixture of the diastereomeric dihydropyrone complexes *rac*-**13a** and *rac*-**13b**. The optimal conditions require



anhydrous $ZnCl_2$ as the Lewis acid mediator. The ^{13}C NMR signals at δ 191, 162, and 107 ppm and the IR stretches at 1680 and 1596 cm^{-1} are indicative of the 2,3-dihydro-4-pyrone substructure. The assignment of the relative stereochemistry at C5 with respect to the dieneiron fragment (i.e., ψ-exo or ψ-endo[26]) is based on a comparison of the signals for H5 of **13a** and **13b** [δ 4.11 (ddd, J = 12.1, 8.9, 5.4) and 4.28 (ddd, J = 11.5, 7.4, 4.3)] with those of the model compounds **14a** and **14b**[10] [δ 4.06 (ddd, J = 11.7, 8.4, 5.4) and 4.21 (ddd, J = 11.4, 7.5, 5.7)]. The formation of **13a** as the major diastereomer corresponds to approach of **12** to the aldehyde carbonyl in the s-cis conformation, on the face opposite to the iron tricarbonyl adjunct. The diastereoisomers **13a** and **13b** are separable by careful column chromatography, and a pure sample of each could be obtained in this fashion; however, it proved more convenient and practical to separate the two diastereomeric series after the next step. Notably, this reaction introduces all 20 carbon atoms and the new asymmetric center at C5 necessary for the 5-HETE skeleton.

Reduction of **13a** or **13b** with DIBAL in C_6H_6 each gave a single alcohol (**15a** and **15b**, 71% and 88%, respectively). Likewise, reduction of a mixture of **13a** and **13b** (2.1:1) gave a mixture of **15a** and **15b** (79%) which was readily separated by column chromatography (pentane–ether (5:2)). The ^1H NMR signal at δ 4.46 ppm, the ^{13}C NMR signals at δ 144 and 105 ppm, and the broad IR stretch at ca. 3600–3300 cm^{-1} are indicative of the hydroxy dihydropyran substructure for both diastereomers. The lack of a large coupling for the H3 signal of both **15a/b** is indicative of its pseudoequatorial orientation.



Ferrier-type rearrangement[27] of **15a** and of **15b** with isopropyl alcohol in the presence of *p*-TsOH gave a single isopropyl acetal in each case (**16a** and **16b**, 73% and 77%, respectively). The ^1H NMR signal at δ 5.10 ppm and the ^{13}C NMR signals at ca. δ 131 and 126 ppm are characteristic for the unsaturated pyranoside fragment. The tendency of the Ferrier rearrangement to produce an axial glucoside is undoubtedly responsible for the formation of a single diastereomer in each case.

Hydrolysis of **16a** and of **16b** was accomplished by transacetalization with acetone in the presence of dilute H_2SO_4 to give the hemiacetals **17a** and **17b** (79% and 82%, respectively). The success of this transformation was dependent on the acid concentration; at too high concentration, an aldehyde byproduct, which was not completely characterized, was formed. Satisfactory results were obtained when the hydrolysis was stopped *before* completion as indicated by TLC monitoring. Thus, in both cases, unreacted starting material was recovered (5% **16a**, 15% **16b**). Notably, the ^1H and ^{13}C NMR spectra of **17a** and **17b** are similar to those of **16a** and **16b**, respectively, except for the disappearance of the signals for the isopropyl group.

Attempted Swern oxidation of **17a** failed, while oxidation with pyridinium dichromate (PDC) gave the desired lactone **18a** (24%) accompanied by the uncomplexed lactone **19** (22%) (vide infra).[24] Oxidation of **17a** with a

(23) Laabassi, M.; Toupet, L.; Gree, R. *Bull. Soc. Chim. Fr.* **1992**, *129*, 47–61.

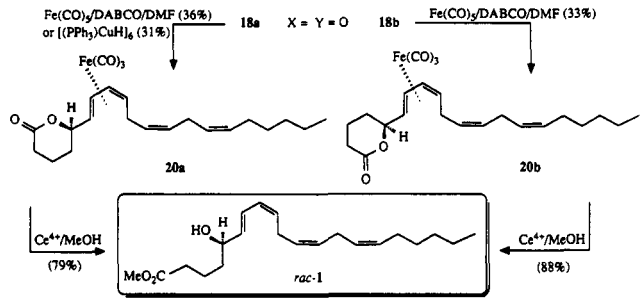
(24) The oxidation of complexes dienols into complexed dienals is acknowledged to be a difficult transformation due to competitive oxidative decomplexation.[8a]

(25) Danishefsky, S. J. *Aldrichem. Acta* **1986**, *19*, 59–69.

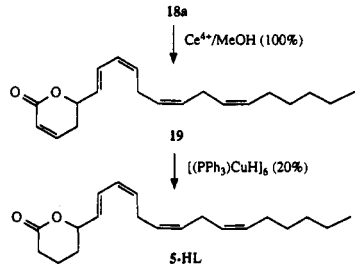
(26) The ψ-exo and ψ-endo nomenclature was first used by Lillya: Clinton, N. A.; Lillya, C. P. *J. Am. Chem. Soc.* **1970**, *92*, 3058–64.

(27) Ferrier, J. P. *J. Chem. Soc.* **1964**, 5443–9.

large excess of MnO_2 (>200 equiv) gave **18a** in good yield (80%). In a similar fashion, oxidation of **17b** under Swern conditions or with PDC were unsuccessful while oxidation with excess MnO_2 gave the unsaturated lactone **18b** (25%). The ^1H NMR signals at δ 6.04 and 6.89 ppm (H2 and H3), the ^{13}C NMR signals at δ 163, 144, and 121 ppm (C1, C3, C2), and the IR stretch at 1723 cm^{-1} are all characteristic of the 2,3-unsaturated δ-lactone fragments of **18a** and **18b**.



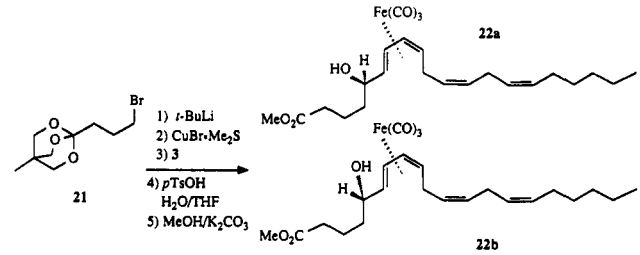
It was previously found in model studies that the reduction of complexed unsaturated lactones, such as **18a/b**, can be somewhat problematic.[10] Reduction of **18a** with $Fe(CO)_5$/DABCO/DMF[28] or with $[(PPh_3)CuH]_6$[29] gave complexed 5-HL **20a** in only modest yield (36% and 31%, respectively). Likewise, reduction of **18b** with $Fe(CO)_5$/DABCO/DMF gave the 5-HL complex **20b** (33%). The ^1H and ^{13}C NMR spectra of **20a** and **20b** are characterized by the disappearance of the signals corresponding to the C2–C3 double bond and the appearance of signals for four additional aliphatic hydrogens and two aliphatic carbons.



The 6*E*,8*Z*,11*Z*,14*Z* stereochemistry of **13a/b**, **15a/b**, **16a/b**, **17a/b**, **18a/b**, and **20a/b** was assigned by comparison of their ^{13}C NMR spectral data with that of the tetraenol **11**. All exhibited signals at ca. δ 130, 129, 128, and 127 ppm corresponding to C11, C12, C14, C15,[30] and those compounds in the **a** (ψ-exo) series exhibited signals at δ 92 and 83 ppm while those in the **b** (ψ-endo) series exhibited signals at δ 89 and 82 ppm corresponding to the coordinated olefinic carbons C7 and C8. Additionally, in all cases the ^1H NMR signal for H5 in the **a** (ψ-exo) series appears upfield of the H5 signal for the corresponding diastereomer in the **b** (ψ-endo) series.[31] It should be noted that the 6*E*,8*Z* stereochemistry, initially generated by nucleophilic addition to cation **2**, is not effected in the hetero Diels–Alder cyclocondensation and that the diene stereochemistry and the stereochemistry at C5 are not altered in subsequent transformations (i.e., reductions, oxidations, and acidic rearrangements/hydrolyses). This is significant since the isomerization of trans,cis-diene complexes to trans,trans-diene complexes has been observed under thermal (ca. 100 °C) as well as acidic conditions.[32]

Oxidative decomplexation of *rac*-**20a** or *rac*-**20b** with ceric ammonium nitrate in methanol gave *rac*-**1** (79% and 88%, respectively). The ^1H and ^{13}C NMR spectra of 5-HETE methyl ester prepared in this fashion were identical with those of an authentic sample generously provided by Dr. R. Zamboni (Merck-Frosst). Since decomplexation of **20a/b** proceeded with concomitent transesterification, we explored an alternative pathway for the preparation of 5-HL. Decomplexation of *rac*-**18a** quantatively gave *rac*-**19**. The IR spectrum of **19** exhibited a strong absorption at 1723 cm^{-1}, and the ^1H NMR spectrum contained signals for 10 olefinic protons. The four corresponding to the conjugated diene appear at δ 6.66 (dd, J = 15.1, 11.0 Hz, H7), 5.99 (t, J = 11.0 Hz, H8), 5.74 (dd, J = 15.1, 6.6 Hz, H6), and 5.49 (dt, J = 11.0, 7.3 Hz, H9); these couplings are indicative of a *trans,cis*-6,8-diene fragment. Reduction of **19** with $[(PPh_3)CuH]_6$ gave 5-HL in an unoptimized 20% yield. The ^1H NMR spectral data for the 5-HL prepared in this fashion was comparable to the literature data.[5b]

Second-Generation Synthesis of 5-HETE Methyl Ester. Due to the length of the preceeding synthesis (11 steps from *rac*-**2**) and the disappointingly low yield for the reduction of the unsaturated lactones **18a/b** or **19** an alternative, shorter synthesis was sought. Nucleophilic addition to a coordinated dienal is known to proceed in a diastereoselective fashion.[33] Application of this approach to **1** requires a protected form of the ester substituent. Bloch et al. have previously reported[5d] on the use of the anion derived from 1-(3-bromopropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**21**)[34] for the introduction of the C1–C4 segment of **1**. The reaction of the anion of **21**

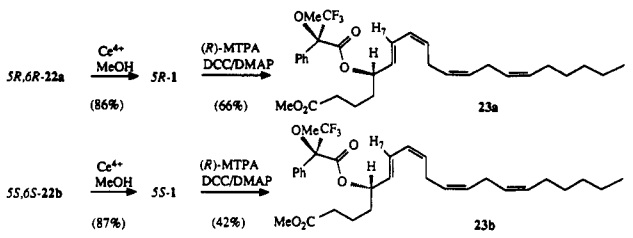


with the key tetraenal *rac*-**3** produced a mixture of diastereomeric alcohols; however, the ortho ester functionality was too labile to allow isolation. Without further purification, the mixture was hydrolyzed (*p*-TsOH/THF/H_2O) and transesterified ($MeOH/K_2CO_3$) to afford a separable mixture of diastereomeric 5-HETE methyl ester complexes *rac*-**22a** and *rac*-**22b** (1.8:1, 56%). The 6*E*,8*Z* stereochemical assignments for both **22a** and **22b** are based on their ^1H and ^{13}C NMR spectral data. In particular, the signals for H7, H8, and H9 of **22a** appear at δ 5.50 (dd, J = 8.0, 5.1 Hz), 5.17 (dd, J = 7.7, 5.1 Hz), and 2.57 (br q, J = 8.0 Hz)[22] and the signals for H7, H8, and H9 for **22b** appear at δ 5.41 (dd, J = 8.2, 5.5 Hz), 5.18 (dd, J = 7.3, 5.5 Hz), and 2.55 (br q, J = 7.3 Hz).[22] Additionally, the signals corresponding to C7 and C8 for **22a** appear at δ 92.1 and 83.3 ppm while the signals corresponding to C7

(28) Noyori, R.; Umeda, I.; Ishigami, T. *J. Org. Chem.* **1972**, *27*, 1542.
(29) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291–3. Brestensky, D. M.; Huseland, D. E.; McGettingan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, *29*, 3749–52.
(30) Assignments to specific carbon atoms are not intended.
(31) It has been empirically observed that the resonance signal for the alcoholic methine proton of ψ-exo dienol complexes, in general, appears upfield of that for the corresponding ψ-endo isomer.[9c,10,25]
(32) Whitesides, T. H.; Neilan, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 63–73.
(33) Gree, R. *Synthesis* **1989**, *341*–56 and references cited therein.
(34) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571.

and C8 for **22b** appear at δ 90.5 and 82.3 ppm (vide supra). The C5 stereochemistry of *rac*-**22a** and *rac*-**22b** (ψ-exo and ψ-endo, respectively) was assigned on the basis of the relative chemical shift for H5 of each diastereomer (δ 3.44 and 3.53, respectively)[31] and upon their relative chromatographic mobility (R_f 0.52 and 0.79, respectively, pentane–Et_2O (1:1)).[35] Confirmation of the C5 and olefin stereochemical assignments was provided by decomplexation in the optically active series. Reaction of (2*R*)-**3** under the same protocol gave a mixture of (5*R*,6*R*)-**22a** and (5S,6R)-**22b** (33% and 21%). Examination of *rac*-**22a** by ^1H NMR spectroscopy in the presence of [Eu(tfc)$_3$] (3.0 equiv, d_6-acetone) indicated partial separation of the broad hydroxyl signals (ca. 0.12 ppm difference). By this method, (5*R*,6*R*)-**22a** was estimated to be >90% ee. Similar analysis of (5*S*,6*R*)-**22b** indicated that it was also >90% ee.

Decomplexation [$(NH_4)_2Ce(NO_2)_6$/MeOH] of *rac*-**22a** and of *rac*-**22b** each gave *rac*-**1**, and decomplexation of (5*R*,6*R*)-**22a** and of (5*S*,6*R*)-**22b** gave the (−)- and (+)-5-HETE methyl esters ((5*R*)-**1** and (5*S*)-**1**, 86% and 87%, respectively). The (5*R*)-**1** prepared in the above fashion gave an optical rotation of $[\alpha]_D = -13.5°$ (*c* 2.0, C_6H_6) and the (5*S*)-**1** gave an optical rotation of $[\alpha]_D = +14.2°$ (*c* 2.0, C_6H_6). When compared to the literature data[6b] ($[\alpha]_D$ = −13.7°, *c* 2.0, C_6H_6, >95% ee, and $[\alpha]_D = +14.4°$, *c* 2.0, C_6H_6, >95% ee) this indicates ≥93% ee for (5*R*)-**1** and ≥98.5% ee for (5*S*)-**1**. Examination of *rac*-**1** by ^1H NMR spectroscopy in the presence of [Eu(tfc)$_3$] using d_6-acetone, $CDCl_3$, or CD_3CN as solvent failed to give satisfactory separation of the signals for the two enantiomers. For this reason, the diastereomeric MPTA esters **23a** and **23b**



were prepared by the literature procedure[6b] (66% and 42%, respectively). The ^1H NMR spectra of **23a** and **23b** in $CDCl_3$ are virtually identical. Fortunately, the ^1H NMR spectra of **23a** and **23b** in d_6-acetone contain clear differences. The signal corresponding to H7 of **23a** appears at δ 6.81, while the signal corresponding to H7 of **23b** appears at δ 6.67. By this method, both **23a** and **23b** were determined to be >90% de.

In summary, the total synthesis of racemic 5-HETE methyl ester has been accomplished by two routes (11 steps and five steps from **2**). Utilizing the latter route, both (−)- and (+)-5-HETE methyl esters were prepared in high optical purity. The stereochemical formation of the trans,cis-diene and of the C5 allylic alcohol center were controlled by a single adjunct, the (tricarbonyl)iron moiety. The methodology outlined above may also be useful for the synthesis of other members of the leukotriene family.

Experimental Section

General Data. All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. All reaction mixtures were dried over anhydrous $MgSO_4$. Spectrograde solvents were used without further purification with the exception of diethyl ether (Et_2O) and tetrahydrofuran (THF) which were distilled from the sodium and potassium benzophenone ketals, respectively, methylene chloride (CH_2Cl_2) which was distilled from phosphorus pentoxide, and hexanes which was fractionally distilled before use. Column chromatography was performed using silica gel 62 (60–200 mesh, Aldrich). "Flash" chromatography[36] was performed using silica gel 60 (230–400 mesh, EM Science). Melting points were obtained using a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on either a Mattson 4020 FTIR or an Analect FX-6200 FTIR spectrometer. Carbon and proton NMR spectra were recorded on a GE Omega GN-300 spectrometer. GC/MS were recorded on a Hewlett-Packard 5890 instrument with a 5970 mass selective detector. The optical rotations for (−)-4, (+)-4, and the diastereomeric ephedrine salts were recorded on an O.C. Randolph polarimeter (Model 539), and the rotations for (*R*)- and (*S*)-5-HETE methyl esters ((5*R*)-**1** and (5*S*)-**1**) were recorded on a JASCO DIP-360 polarimeter. Elemental analyses were sent to Midwest Microlabs, Indianapolis, IN, and high-resolution mass spectra were obtained from the Midwest Center for Mass Spectrometry.

Tricarbonyl(methyl 6-oxohexa-2(*E*),4(*E*)-dienoate)iron (*rac*-4). To a solution of methyl 6-oxohexa-2(*E*),4(*E*)-dienoate (0.44 g, 3.14 mmol) in toluene (10 mL) was added iron nonacarbonyl (1.37 g, 3.77 mmol). The mixture was heated at reflux for 2 h, filtered through Celite, and washed with CH_2Cl_2. The combined organic solvents were concentrated under reduced pressure to afford a crude product, which was purified by column chromatography (hexanes–ethyl acetate (5:1)) to give the known **4**[12,13] as a yellow crystalline solid (0.72 g, 81%): mp 82–83 °C (lit.[12b] mp 90 °C); ^1H NMR ($CDCl_3$) δ 9.43 (d, *J* = 3.2 Hz, 1 H), 6.06 (dd, *J* = 8.2, 5.4 Hz, 1 H), 5.99 (dd, *J* = 8.0, 5.4 Hz, 1 H), 3.69 (s, 3 H), 1.53 (dd, *J* = 8.2, 3.2 Hz, 1 H), 1.47 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 205.7, 196.3, 172.3, 88.5, 85.3, 61.0, 55.6, 52.7. The ^1H NMR spectral data matches the literature values.[13b]

Resolution of 4.[12b] To a solution of racemic complex **4** (14.5 g, 51.8 mmol) in anhydrous CH_2Cl_2 (500 mL) was added (−)-ephedrine (8.5 g, 51.8 mmol, Fluka) and 4A molecular sieves (38.8 g). The reaction mixture was maintained at rt for 16 h in the absence of light. After filtration and evaporation of the solvent, the residue was dissolved in anhydrous Et_2O (40 mL). The (+)-diastereomer crystallized as light red cubic crystals at −15 °C. After collection of the crystals, the solvent was removed and the residue dissolved in anhydrous hexanes (30 mL). The (−)-diastereomer crystallized as yellow needles at rt. Subsequent alternating crystallizations in Et_2O followed by hexanes were carried out an additional three times. The combined crops of the (+)-diastereoisomer were recrystallized from Et_2O (10.3 g, 90%), and the combined crops of the (−)-diastereomer were recrystallized from hexane (10.1 g, 89%).

(+)-Diastereomer: mp 109–110 °C (lit.[12] mp 111 °C); ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.93 (dd, *J* = 8.3, 5.4 Hz, 1 H), 5.71 (dd, *J* = 8.5, 5.4 Hz, 1 H), 4.99 (d, *J* = 7.1 Hz, 1 H), 3.88 (d, *J* = 5.0 Hz, 1 H), 3.68 (s, 3 H), 2.86 (pent, *J* = 7.1 Hz, 1 H), 2.41 (s, 3 H), 1.46 (dd, *J* = 8.5, 5.0 Hz, 1 H), 1.12 (d, *J* = 8.3 Hz, 1 H), 0.69 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.2, 172.3, 139.4, 127.9 (2 C), 127.6 (3 C), 97.2, 84.6 (2 C), 81.9, 64.6, 60.6, 51.6, 46.3, 36.7, 14.8; IR (CH_2Cl_2) 2067, 1983, 1713 cm^{-1}; $[\alpha]_D = +104°$ (*c* 0.060, MeOH) (lit.[12] $[\alpha]_D$ +100° (*c* 0.069, MeOH)).

(−)-Diastereomer: mp 103–104 °C (lit.[12] mp 104 °C); ^1H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 5.89 (ddd, *J* = 8.1, 5.3, 0.8 Hz, 1 H), 5.45 (ddd, *J* = 8.5, 5.3, 1.0 Hz, 1 H), 5.03 (d, *J* = 8.0 Hz, 1 H), 3.68 (s, 3 H), 3.51 (d, *J* = 8.5 Hz, 1 H), 2.89 (dq, *J* = 8.0, 6.3 Hz, 1 H), 2.33 (s, 3 H), 1.39 (td, *J* = 8.5, 0.8 Hz, 1 H), 1.18 (dd, *J* = 8.1, 1.0 Hz, 1 H), 0.66 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 212.3, 172.5, 139.5, 127.8 (2 C), 127.5, 127.3 (2 C), 100.0, 86.1, 84.4, 81.8, 64.6, 61.0, 51.7, 35.8, 15.1; IR (CH_2Cl_2) 2065, 2001, 1713 cm^{-1}; $[\alpha]_D = -363°$ (*c* 0.100, MeOH) (lit.[12] $[\alpha]_D = -365°$ (*c* 0.12, MeOH)).

Tricarbonyl((2*R*,5*S*)-methyl 6-oxohexa-2(*E*),4(*E*)-dienoate)iron ((−)-4). To a suspension of SiO_2 (90 g) in CH_2Cl_2 (250 mL) was added with stirring H_2O (9 g). After the water

(35) It has been empirically found that ψ-exo diastereomeric alcohols are in general less mobile than their ψ-endo counterparts: Gresham, D. G.; Lillya, C. P.; Uden, P. C.; Walters, F. H. *J. Organomet. Chem.* **1977**, *142*, 123–31.

(36) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–5.

phase had disappeared, a solution of the (−)-diastereomeric oxazoline (9.6 g) in a small amount of CH_2Cl_2 was added in the absence of light at rt. After being stirred for 7 h, the mixture was filtered and washed with CH_2Cl_2. The solvent was evaporated and the residue dissolved in anhydrous Et_2O (6 mL) and stored at −15 °C for crystallization. Light red cubic crystals of (−)-**4** were collected and washed with cold Et_2O (5.19 g, 92%). The NMR data were identical with those values of *rac*-**4**. Analysis by ^1H NMR spectroscopy in the presence of a chiral shift reagent (Eu[thf]$_3$, d_6-acetone) indicated that the product was >94% ee: $[\alpha]_D$ = −55° (*c* 0.10 MeOH) (lit.[12] $[\alpha]_D$ = −62° (*c* 0.1, MeOH)).

Tricarbonyl[(2*S*,5*R*)-methyl (2-5-η)-6-oxo-2(*E*),4(*E*)-hexa-2,4-dienoate]iron ((+)-4) was prepared from the (+)-diastereomeric oxazoline in 94% yield in the same fashion as the preparation of (−)-**4**. Analysis by ^1H NMR spectroscopy in the presence of a chiral shift reagent (Eu[thf]$_3$, d_6-acetone) indicated that the product was >94% ee: $[\alpha]_D$ = +63° (*c* 0.10 MeOH) (lit.[12] $[\alpha]_D$ = +62° (*c* 0.1, MeOH)).

Tricarbonyl(methyl 6-hydroxyhexa-2(*E*),4(*E*)-dienoate)-iron (*rac*-5). To a solution of *rac*-**4** (1.14 g, 4.07 mmol) in anhydrous EtOH (15 mL) was added a mixture of KBH_4 (0.26 g, 4.88 mmol) in anhydrous EtOH (15 mL) at rt. The mixture was stirred for 20 min. To the reaction mixture was added H_2O (2 mL), and the mixture was stirred for an additional 10 min and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were filtered through filter-aid, dried, and concentrated to afford a yellow oil which was purified by column chromatography (hexanes–ethyl acetate (25:4)) to give **5** as a yellow oil (1.06 g, 92%). The ^1H, ^{13}C and IR spectra were identical to the literature values.[12]

Tricarbonyl(2*R*,5*S*)-methyl 6-hydroxyhexa-2(*E*),4(*E*)-dienoate)iron ((2*R*,5*S*)-5). The preparation of (2*R*,5*S*)-**5** from (−)-**4** was carried out in the same fashion as the preparation of *rac*-**5** (95%). Analysis by ^1H NMR spectroscopy in the presence of a chiral shift reagent (Eu[thf]$_3$, d_6-acetone) indicated that the product was >90% ee.

Tricarbonyl[η^5-1-(methoxycarbonyl)pentadienyl]iron-(1+) Hexafluorophosphate (*rac*-2). To a mixture of acetic anhydride (15 mL) and hexafluorophosphoric acid (60% w/w solution, 11.9 g) at 0–5 °C was added dropwise a cold solution of *rac*-**5** (6.82 g, 24.4 mmol) and acetic anhydride (7 mL) in Et_2O (35 mL). After addition, the mixture was stirred for 30 min and a pale brown precipitate appeared. The mixture was added dropwise to excess Et_2O (1000 mL) to induce precipitation, filtered, and dried in vacuo to give **2** as a pale yellow solid (6.62 g, 66%). *rac*-**2**: mp 134–140 °C: 300-MHz ^1H NMR (CD_3NO_2) δ 7.15 (td, *J* = 7.0, 1.0 Hz, 1 H), 6.77 (dd, *J* = 6.9, 11.0, 1 H), 6.45 (ddd, *J* = 6.9, 10.2, 13.1, 1 H), 4.10 (ddd, *J* = 1.0, 3.7, 10.0 Hz, 1 H), 3.89 (s, OCH_3), 2.64 (dd, *J* = 3.7, 13.0, 1 H), 2.63 (d, *J* = 11.0, 1 H); 15 MHz ^{13}C NMR (CD_3NO_2) δ 195.2, 168.1, 106.2, 105.8, 97.9, 68.5, 64.9, 52.8; IR (Nujol) 2131, 2081, 1720 cm^{-1}. Anal. Calcd for $C_{10}H_9O_5FePF_6 \cdot {}^1/_2H_2O$: C, 28.66; H, 2.40. Found: C, 28.47; H, 2.26.

Tricarbonyl[(1*R*)-η^5-1-(methoxycarbonyl)pentadienyl]-iron(1+) Hexafluorophosphate ((1*R*)-2). To a mixture of acetic anhydride (8 mL) and hexafluorophosphoric acid (60% w/w solution, 6.3 g) at −15 °C was added a cold mixture of (2*R*,5*S*)-**5** (3.60 g, 12.8 mmol) and acetic anhydride (4 mL) in dry Et_2O (18 mL). After addition, the mixture was stirred for 10 min and allowed to warm to 0 °C. The mixture was stirred for 30 min, and then anhydrous Et_2O (30 mL) was added and a pale brown precipitate appeared at the bottom. After filtration, the precipitate was washed with anhydrous ether and dried in vacuo to give (1*R*)-**2** as a pale yellow solid (4.20 g, 80%). All spectra data were identical with those of *rac*-**2**.

Reaction of *rac*-2 with (*S*)-Methyl Lactate. To a solution of (*S*)-methyl lactate (25 mg, 0.24 mmol) in dry CH_2Cl_2 (3 mL) at rt was added *rac*-**2** (50 mg, 0.12 mmol) in one portion. The mixture was stirred for 1 h, and then H_2O (1 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL), and the combined extracts were dried and concentrated. The residue was purified by flash chromatography (hexanes–ethyl acetate (5:1)) to give a 1:1 mixture of **6a** and **6b** as a yellow oil (15 mg, 33%): ^1H NMR (C_6D_6) δ 5.47 (m, 1 H), 4.83 (dd, *J* = 8.7, 5.0 Hz, $^1/_2$ H, **6a**), 4.71 (dd, *J* = 8.7, 5.0 Hz, $^1/_2$ H, **6b**), 3.64 (q, *J* = 6.9 Hz, **6a**) and 3.63 (q, *J* = 6.9 Hz, **6b**) total 1 H, 3.48 (dd, *J* = 10.4, 6.2 Hz, **6b**) and 3.45 (dd, *J* = 11.4, 5.2 Hz, **6a**) total 1 H, 3.31 and 3.30 (2s, 3 H), 3.29 (s, 3 H), 3.06 (dd, *J* = 11.4, 5.2 Hz, $^1/_2$ H, **6a**), 2.93 (dd, *J* = 10.6, 5.8 Hz, $^1/_2$ H, **6b**), 1.27 (2d, both *J* = 6.9 Hz, 3 H), 1.01–0.83 (m, 2 H).

Reaction of Cation (2*R*)-2 with (*S*)-Methyl Lactate. The reaction of (2*R*)-**2** with (*S*)-methyl lactate was carried out in the same fashion as the reaction of *rac*-**2**. The residue was purified by flash chromatography (hexanes–ethyl acetate (5:1)) to give **6a** as a yellow oil (20 mg, 45%): ^1H NMR (C_6D_6) δ 5.49 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1 H), 4.83 (dd, *J* = 8.7, 5.0 Hz, 1 H), 3.64 (q, *J* = 6.9 Hz, 1 H), 3.45 (dd, *J* = 11.4, 5.2 Hz, 1 H), 3.31 (s, 3 H), 3.29 (s, 3 H), 3.06 (dd, *J* = 11.4, 5.2 Hz, 1 H), 1.27 (d, *J* = 6.9 Hz, 3 H), 0.91 (dt, *J* = 8.7, 5.2 Hz, 1 H), 0.85 (dd, *J* = 8.0, 1.0 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 210.0, 172.7, 172.1, 85.2, 83.8, 74.9, 70.2, 60.3, 51.2, 51.1, 46.4, 18.4; IR (CH_2Cl_2) 2064, 1993, 1749, 1712 cm^{-1}.

Tricarbonyl[methyl (2-5-η)-hexadeca-2(*E*),4(*Z*)-diene-7,10-diynoate]iron (*rac*-7). To a solution of freshly distilled 1,4-decadiyne[37] (15.2 g, 0.11 mol) in Et_2O–THF (4:1, 560 mL) at −45 °C was added dropwise a solution of *n*-butyllithium (2.5 M in hexane, 45 mL, 0.11 mol). The mixture was stirred for 15 min, and then CuBr·Me_2S (7.60 g, 37 mmol) was added. After the mixture was stirred for 15 min, the solid cation *rac*-**2** (9.13 g, 22.0 mmol) was added in one portion. The system was stirred for 4 h at −45 °C. Saturated aqueous NH_4Cl (200 mL) was added to quench the reaction, and the mixture was warmed to rt. The mixture was extracted with CH_2Cl_2 (800 mL), and the organic layer was washed with saturated aqueous NH_4Cl (3 × 150 mL) and H_2O (3 × 100 mL) until it was neutral. The organic layer was dried, filtered through filter-aid, and concentrated. The residue was purified by column chromatography (hexanes–Et_2O (20:1)) to afford *rac*-**7** as a yellow oil (6.15 g, 69%): ^1H NMR ($CDCl_3$) δ 6.06 (ddd, *J* = 8.8, 5.4, 1.2 Hz, 1 H), 5.32 (dd, *J* = 7.5, 5.4 Hz, 1 H), 3.68 (s, 3 H), 3.13 (pent, *J* = 2.4 Hz, 2 H), 2.89 (qd, *J* = 7.7, 1.2 Hz, 1 H), 2.15 (tt, *J* = 7.1, 2.4 Hz, 2 H), 2.10 (m, 2 H), 1.48 (pent, *J* = 7.1 Hz, 2 H), 1.32 (m, 5 H), 0.89 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 212.8, 173.6, 94.2, 85.7, 81.4, 79.4, 77.1, 74.4, 57.3, 52.8, 46.3, 31.7, 29.0, 22.8, 19.3, 19.1, 14.6, 10.3; IR (CH_2Cl_2) 2070, 1991, 1713 cm^{-1}; HRMS *m/z* 314.0972 [calcd for $C_{17}H_{22}O_2Fe$ (M − 3 CO), *m/z* 314.0966].

Tricarbonyl[(2*R*)-methyl (2-5-η)-hexadeca-2(*E*),4(*Z*)-diene-7,10-diynoate]iron (2*R*-7). To a solution of freshly distilled 1,4-decadiyne (9.20 g, 68.6 mmol) in Et_2O–THF (4:1, 300 mL) at −78 °C was added dropwise *n*-butyllithium (1.6 M in hexane, 43 mL, 68.6 mmol), and the mixture was stirred for 15 min. The mixture was warmed to −45 °C, and CuBr·Me_2S (4.70 g, 22.9 mmol) was added. The mixture was stirred for 20 min at −45 °C and the solid cation (2*R*)-**2** (3.75 g, 9.15 mmol) was added in one portion. The system was stirred for 4 h at −45 °C. After the same workup as before, purification by flash chromatography (hexanes–Et_2O (25:1)) gave (2*R*)-**7** as a yellow oil (2.34 g, 64%). All the spectral data are identical with those values of the racemic compound. Analysis by ^1H NMR spectroscopy in the presence of a chiral shift reagent (Eu[tfc]$_3$, d_6-acetone) indicated that the product was >92% ee.

Tricarbonyl[(2-5-η)-hexadeca-2(*E*),4(*Z*)-diene-7,10-diynol]iron (*rac*-8). To a solution of *rac*-**7** (0.15 g, 0.38 mmol) in CH_2Cl_2 (5 mL) at rt was added dropwise DIBAL (1 M in toluene, 0.75 mL, 0.75 mmol). After the addition was complete the mixture was stirred for 15 min, and then H_2O (1 mL) was added. The mixture was stirred 5 min, and more H_2O (3 mL) was added followed by CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried, and concentrated. The residue was purified by column chromatography (hexanes–ethyl acetate (20:3)) to give *rac*-**8** as a yellow oil (60 mg, 43%): ^1H NMR ($CDCl_3$) δ 5.46 (dd, *J* = 8.7, 5.2 Hz, 1 H), 5.21 (dd, *J* = 7.4, 5.2 Hz, 1 H), 3.83 (m, 1 H), 3.65 (m, 1 H), 3.13 (pent, *J* = 2.4 Hz, 2 H), 2.75 (q, *J* = 7.7 Hz, 1 H), 2.23 (m, 2 H), 2.15 (tt, *J* = 7.1, 2.2 Hz, 2 H), 1.61 (s br, 1 H), 1.48 (pent, *J* = 7.1 Hz, 2 H), 1.31 (m, 5 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.9, 93.7, 83.5, 81.5, 80.1, 76.6, 74.6, 66.3, 61.1, 56.7, 31.6, 29.1,

(37) Gensler, W. J.; Mahadevan, A. P.; Casella, J., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 163–7.

22.8, 19.3, 18.9, 14.6, 10.4; IR (neat) 3572–3381, 2054, 1967 cm^{-1}; HRMS *m/z* 314.0958 [calcd for $C_{17}H_{22}O_2Fe$ (M – 2 CO), *m/z* 314.0966].

Tricarbonyl[(2–5-η)-hexadeca-2(*E*),4(*Z*)-diene-7,10-diynal]iron (*rac*-9). To a solution of *rac*-8 (100 mg, 0.27 mmol) in CH_2Cl_2 (10 mL) was added pyridium dichromate (198 mg, 0.54 mmol) and activated 3Å molecular sieves (80 mg) followed by a drop of anhydrous acetic acid. The mixture was stirred for 6 h and worked up as before. The crude product was purified by column chromatography (hexanes–Et_2O (10:1)) to afford *rac*-9 as a yellow oil (50 mg, 50%): ^1H NMR ($CDCl_3$) δ 9.37 (d, *J* = 3.6 Hz, 1 H), 6.06 (ddd, *J* = 8.7, 5.4, 1.2 Hz, 1 H), 5.40 (dd, *J* = 7.3, 5.4 Hz, 1 H), 3.15 (pent, *J* = 2.4 Hz, 2 H), 3.05 (qd, *J* = 8.1, 1.2 Hz, 1 H), 2.41 (ddd, *J* = 8.7, 3.6, 0.8 Hz, 1 H), 2.22 (qd, *J* = 8.1, 1.2 Hz, 2 H), 2.16 (tt, *J* = 6.9, 2.4 Hz, 2 H), 1.5 (m, 2 H), 1.33 (m, 4 H), 0.90 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.0, 197.3, 92.5, 86.9, 77.5, 74.3, 66.5, 58.4, 55.0, 31.7, 29.1, 22.9, 19.4, 19.3, 15.9, 14.6, 10.4. This compound was extremely unstable and therefore was not further characterized.

Tricarbonyl[methyl (2–5-η)-hexadeca-2(*E*),4(*Z*),7(*Z*),10-(*Z*)-tetraenoate]iron (*rac*-10). A solution of *rac*-7 (2.46 g, 6.18 mmol) and Lindlar catalyst (250 mg, Aldrich) in CH_2Cl_2 (90 mL) was shaken under H_2 atmosphere (18 psi) in a Parr hydrogenation apparatus for 30 min. The mixture was filtered through a bed of filter-aid, the bed was washed with CH_2Cl_2, and the combined organic phases were concentrated. The residue was purified by column chromatography (hexanes–Et_2O (100:3)) to give *rac*-10 as a yellow oil (2.47 g, 99%): ^1H NMR ($CDCl_3$) δ 6.07 (ddd, *J* = 8.7, 5.4, 1.0 Hz, 1 H), 5.35 (m, 5 H), 3.69 (s, 3 H), 2.72 (m, 2 H), 2.30 (br dt, *J* = 14.3, 6.0 Hz, 1 H), 2.23 (dd, *J* = 8.5, 1.0 Hz, 1 H), 2.03 (br q, *J* = 6.7 Hz, 2 H), 1.89 (m, 1 H), 1.31 (m, 7 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.9, 173.0, 130.6, 129.1, 128.9, 127.0, 92.8, 85.3, 59.8, 51.5, 45.8, 31.4, 29.2, 27.2, 26.5, 25.5, 22.5, 14.0; IR (neat) 2061, 2001, 1718 cm^{-1}; HRMS *m/z* 318.1275 [calcd for $C_{17}H_{26}O_2Fe$ (M – 3 CO), *m/z* 318.1277].

Tricarbonyl[(2*R*)-methyl (2–5-η)-Hexadeca-2(*E*),4(*Z*),7-(*Z*),10(*Z*)-tetraenoate]iron ((2*R*)-10). This compound was made from (2*R*)-7 in the same fashion as the preparation of *rac*-10 (91%). All the spectral data are identical with those values of the racemic compound. Analysis by ^1H NMR spectroscopy in the presence of a chiral shift reagent (Eu[tfc]$_3$, d_6-acetone) indicated that the product was >90% ee.

Tricarbonyl[(2–5-η)-hexadeca-2(*E*),4(*Z*),7(*Z*),10(*Z*)-tetraen-1-ol]iron (*rac*-11). To a solution of *rac*-10 (0.47 g, 1.17 mmol) in CH_2Cl_2 (40 mL) was added dropwise a solution of DIBAL (1 M in toluene, 2.34 mL, 2.34 mmol). The mixture was stirred for 10 min, quenched with methanol, poured into saturated aqueous Na_2SO_4 (10 mL), and extracted with Et_2O. The combined organic layers were dried and concentrated. The residue was purified by column chromatography (hexanes–Et_2O (1:1)) to give *rac*-11 as a yellow oil (0.38 g, 87%): ^1H NMR ($CDCl_3$) δ 5.44–5.29 (m, 5 H), 5.19 (dd, *J* = 7.3, 5.0 Hz, 1 H), 3.80 (br m, 1 H), 3.67 (br m, 1 H), 2.70 (t, *J* = 6.1 Hz, 1 H), 2.59 (m, 1 H), 2.31 (m, 2 H), 2.03 (br q, *J* = 6.5 Hz, 2 H), 1.91 (m, 1 H), 1.57 (br s, 1 H), 1.30 (m, 7 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.9, 130.6, 129.7, 128.5, 127.2, 92.4, 83.3, 65.7, 60.7, 59.7, 31.4, 29.2, 27.2, 26.4, 25.5, 22.5, 14.0; IR (neat) 3329 (br), 2043, 1967 cm^{-1}; HRMS *m/z* 318.1277 [Calcd for $C_{17}H_{26}O_2Fe$ (M – 2 CO), *m/z* 318.1278].

Tricarbonyl[(2–5-η)-hexadeca-2(*E*),4(*Z*),7(*Z*),10(*Z*)-tetraenal]iron (*rac*-3). To a solution of *rac*-11 (0.64 g, 1.71 mmol) in acetone (15 mL) at rt was added with vigorous stirring activated MnO_2 (3.3 g). After 36 h, the mixture was filtered through filter-aid and washed several times with acetone, and the combined organic fractions were evaporated. The residue was purified by column chromatography (hexanes–Et_2O (100:3)) to afford *rac*-3 as a yellow oil (0.44 g, 69%): ^1H NMR ($CDCl_3$) δ 9.34 (d, *J* = 3.9 Hz, 1 H), 6.05 (ddd, *J* = 8.7, 5.2 Hz, 1 H), 5.38 (m, 5 H), 2.89 (br q, *J* = 7.5 Hz, 1 H), 2.72 (t, *J* = 6.7 Hz, 1 H), 2.50 (dd, *J* = 8.7, 3.8 Hz, 1 H), 2.36 (dt, *J* = 15.1, 6.3 Hz, 1 H), 2.02 (br q, *J* = 6.7 Hz, 2 H), 1.95 (m, 1 H), 1.29 (m, 7 H), 0.89 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.7, 196.6, 130.2, 129.3, 128.8, 126.9, 91.1, 86.6, 61.1, 54.7, 31.4, 29.2, 27.2, 26.9, 25.6, 22.5, 14.0; IR (neat) 2062, 1983, 1684 cm^{-1}; HRMS *m/z* 288.1176 [calcd for $C_{16}H_{24}OFe$ (M – 3 CO), *m/z* 288.1173].

Tricarbonyl[(2*R*)-(2–5-η)-hexadeca-2(*E*),4(*Z*),7(*Z*),10(*Z*)-tetraenal]iron ((2*R*)-3). To a solution of (2*R*)-10 (2.01 g, 4.9 mmol) in dry CH_2Cl_2 (150 mL) at –5 °C was added DIBAL (1 M in toluene, 9.8 mL, 9.8 mmol). The mixture was stirred for 10 min and worked up as before. After removal of the solvent, the residue was dissolved in acetone (100 mL), and activated MnO_2 (34.5 g) was added at rt. The mixture was stirred for 30 min and filtered, the filter bed was washed with acetone, and the combined organic layers were evaporated. The residue was purified by flash chromatography (hexanes–ethyl acetate (5:1)) to afford (2*R*)-3 as a yellow oil (1.21 g, 65%). All the spectral data are identical with those values of the racemic compound.

Tricarbonyl[(2*R,1′*R**,4′*R**)- and (2*S**,1′*R**,4′*R**)-2,3-dihydro-2-[(1′–4′-η)-pentadeca-1′(*E*),3′(*Z*),6′(*Z*),9′(*Z*)-tetraenyl]-4*H*-pyran-4-one]iron (13a and 13b).** To a solution of *rac*-3 (3.33 g, 8.95 mmol) and 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (12) (6.16 g, 35.8 mmol, Aldrich) in dry THF (90 mL) at rt was added anhydrous $ZnCl_2$ (4.87 g, 35.8 mmol). The mixture was stirred for 46 h. The reaction was quenched by adding saturated aqueous $NaHCO_3$ (15 mL), and the mixture was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried and concentrated. The residue was dissolved in CH_2Cl_2 (80 mL), and CF_3CO_2H (5 mL) was added. The dark red solution was stirred at rt for 2 h. To the solution was added saturated aqueous $NaHCO_3$ (10 mL), and the mixture was extracted with Et_2O. The combined organic layers were dried and concentrated. The residue was purified by flash column chromatography (hexanes–ethyl acetate (4:1)) to give a mixture of **13a** and **13b** (2.1:1) as a yellow oil (3.39 g, 86%). The mixture could be separated by further chromatography (pentane–Et_2O (10:3)) to give **13a** as a yellow oil, followed by **13b** as a yellow oil; however, it proved more convenient to separate the mixture after the next step.

13a: R_f 0.46 (hexanes–ethyl acetate (7:3)); ^1H NMR ($CDCl_3$) δ 7.35 (d, *J* = 5.9 Hz, 1 H), 5.56 (ddd, *J* = 8.5, 5.2, 1.2 Hz, 1 H), 5.44 (d, *J* = 5.9 Hz, 1 H), 5.31 (m, 4 H), 5.25 (dd, *J* = 7.5, 5.4 Hz, 1 H), 4.11 (ddd, *J* = 12.1, 8.9, 5.4 Hz, 1 H), 2.68 (m, 4 H), 2.28 (dt, *J* = 14.9, 6.2 Hz, 1 H), 2.13 (td, *J* = 9.0, 0.9 Hz, 1 H), 2.03 (br q, *J* = 6.9 Hz, 2 H), 1.89 (ddd, *J* = 14.3, 9.6, 6.2 Hz, 1 H), 1.29 (m, 7 H), 0.89 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.8, 191.7, 162.9, 130.7, 129.2, 128.9, 127.0, 107.1, 92.3, 84.6, 83.0, 60.2, 57.2, 43.1, 31.5, 29.2, 27.2, 26.4, 25.6, 22.5, 14.0; IR (neat) 2051, 1975, 1683, 1596 cm^{-1}; HRMS *m/z* 356.1455 [calcd for $C_{20}H_{28}O_3Fe$ (M – 3 CO), *m/z* 356.1434].

13b: R_f 0.36 (hexanes–ethyl acetate (7:3)); ^1H NMR ($CDCl_3$) δ 7.39 (d, *J* = 6.0 Hz, 1 H), 5.47 (dd, *J* = 8.7, 5.4 Hz, 1 H), 5.43 (d, *J* = 6.0 Hz, 1 H), 5.33 (m, 4 H), 5.23 (dd, *J* = 7.7, 4.9 Hz, 1 H), 4.28 (ddd, *J* = 11.5, 7.4, 4.3 Hz, 1 H), 2.67 (m, 4 H), 2.26 (dt, *J* = 14.5, 6.1 Hz, 1 H), 2.20 (t, *J* = 7.8 Hz, 1 H), 2.04 (br q, *J* = 6.6 Hz, 2 H), 1.85 (ddd, *J* = 14.5, 9.5, 4.8 Hz, 1 H), 1.29 (m, 7 H), 0.89 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.4, 191.5, 162.8, 130.7, 129.4, 128.7, 127.0, 107.2, 89.6, 83.4, 81.5, 59.7, 59.0, 44.7, 31.4, 29.2, 27.2, 26.1, 25.5, 22.5, 14.0; IR (neat) 2059, 1975, 1689, 1596 cm^{-1}; HRMS *m/z* 356.1432 [calcd for $C_{20}H_{28}O_2Fe$ (M – 3 CO), *m/z* 356.1434].

Cyclocondensation Catalyzed by BF_3/Ether. To a solution of *rac*-3 (0.65 g, 1.75 mmol) and 12 (1.20 g, 6.99 mmol) in dry Et_2O (20 mL) at –78 °C was added dropwise BF_3·Et_2O (0.86 mL, 6.99 mmol). After being stirred at –78 °C for 8 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (2 mL) and allowed to warm to rt. The mixture was diluted with brine and extracted with Et_2O, and the combined organic layers were dried and concentrated. The residue was dissolved in CH_2Cl_2 (15 mL) and treated with CF_3CO_2H (10 drops). The mixture was stirred for 12 h and worked up as before. Purification of the residue by column chromatography (hexanes–ethyl acetate (4:1)) gave a yellow oil (0.26 g, 34%), which was determined to be a mixture of **13a** and **13b** (1:4.7) by ^1H NMR spectroscopy.

Cyclocondensation Catalyzed by BF_3/CH_2Cl_2. To a solution of *rac*-3 (185 mg, 0.50 mmol) and 12 (345 mg, 2.0 mmol) in dry CH_2Cl_2 (6 mL) at –78 °C was added dropwise BF_3·OEt_2 (0.12 mL, 1.0 mmol). The mixture was stirred for 6 h and worked up as before. The residue was dissolved in CH_2Cl_2 (5 mL) and treated with CF_3CO_2H (5 drops). After being stirred for 6 h, the reaction mixture was worked up in the above fashion. Purification of the residue by column chromatography (hexanes–ethyl acetate

(4:1)) afforded a yellow oil (68 mg, 31%), which was determined to be a mixture of **13a** and **13b** (1:2.6) by ^{1}H NMR spectroscopy.

Cyclocondensation Catalyzed by $TiCl_4$. To a solution of *rac*-**3** (185 mg, 0.50 mmol) in CH_2Cl_2 (6 mL) at −78 °C was added a solution of $TiCl_4$ (1 M in toluene, 0.50 mL, 0.50 mmol). The mixture was stirred for 5 min, and **12** (344 mg, 2.0 mmol) was added. After the mixture was stirred for 7 h at −78 °C, saturated aqueous $NaHCO_3$ (0.5 mL) was added, the mixture was warmed to rt and extracted with Et_2O (3 × 30 mL), and the combined organic phases were washed with brine, dried, and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL), and CF_3CO_2H (3 drops) was added. The mixture was stirred for 6 h and worked up as before. Purification of the residue by column chromatography (hexanes–ethyl acetate (4:1)) gave a yellow oil (50 mg, 23%), which was determined to be a mixture of **13a** and **13b** (1:5.9) by ^{1}H NMR spectroscopy.

Tricarbonyl[(2*R,1′*R**,4′*R**)-2,3-dihydro-2-[(1′–4′-η)-pentadeca-1′(*E*),3′(*Z*),6′(*Z*),9′(*Z*)-tetraenyl]-4-hydroxy-4*H*-pyran]iron (15a).** To a solution of *rac*-**13a** (445 mg, 1.01 mmol) in dry C_6H_6 (25 mL) at 0–5 °C was added dropwise a solution of DIBAL (1 M in CH_2Cl_2, 2.0 mL, 2.0 mmol). The mixture was stirred for 20 min and was then quenched with methanol (1 mL). Saturated aqueous Na_2SO_4 (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 80 mL). The combined organic layers were dried and concentrated. The residue was purified by column chromatography (pentane–Et_2O (5:1)) to give **15a** as a yellow oil (320 mg, 71%): ^{1}H NMR ($CDCl_3$) δ 6.37 (d, *J* = 6.0 Hz, 1 H), 5.50 (dd, *J* = 8.3, 5.2 Hz, 1 H), 5.35 (m, 4 H), 5.21 (dd, *J* = 7.4, 5.2 Hz, 1 H), 4.79 (dt, *J* = 6.0, 1.6 Hz, 1 H), 4.46 (br t, *J* = 7.6 Hz, 1 H), 3.68 (ddd, *J* = 11.1, 8.5, 1.6 Hz, 1 H), 2.70 (t, *J* = 6.4 Hz, 1 H), 2.62 (br q, *J* = 7.6 Hz, 1 H), 2.38 (dd, *J* = 13.3, 6.4 Hz, 1 H), 2.29 (m, 2 H), 2.04 (br q, *J* = 6.6 Hz, 2 H), 1.95 (m, 1 H), 1.83 (m, 1 H), 1.52 (s br, 1 H), 1.29 (m, 7 H), 0.89 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.4, 144.8, 130.6, 129.5, 128.7, 127.1, 105.2, 92.7, 83.8, 78.1, 62.8, 60.5, 59.8, 39.2, 31.4, 29.2, 27.2, 26.4, 25.6, 22.5, 14.0; IR (CH_2Cl_2) 3601 (br), 2047, 1980, 1644 cm^{-1}; HRMS *m/z* 358.1603 [calcd for $C_{20}H_{30}O_2Fe$ (M − 3 CO), *m/z* 358.1590].

Tricarbonyl[(2*S,1′*R**,4′*R**)-2,3-dihydro-2-[(1′–4′-η)-pentadeca-1′(*E*),3′(*Z*),6′(*Z*),9′(*Z*)-tetraenyl]-4-hydroxy-4*H*-pyran]iron (15b).** The reduction of **13b** was performed in the same fashion as for the reduction of **13a**. Purification by column chromatography (hexanes–ethyl acetate (4:1)) gave **15b** as a yellow oil (40 mg, 88%): ^{1}H NMR ($CDCl_3$) δ 6.37 (d, *J* = 6.0 Hz, 1 H), 5.48 (dd, *J* = 8.1, 5.2 Hz, 1 H), 5.32 (m, 4 H), 5.17 (dd, *J* = 7.7, 5.2 Hz, 1 H), 4.77 (dt, *J* = 6.0, 1.8 Hz, 1 H), 4.46 (br s, $^1/_2W$ = 21 Hz, 1 H), 3.98 (ddd, *J* = 11.1, 6.0, 1.8 Hz, 1 H), 2.69 (t, *J* = 6.1 Hz, 1 H), 2.53 (ddt, *J* = 8.1, 1.6, 7.2 Hz, 1 H), 2.29 (m, 3 H), 2.04 (br q, *J* = 6.6 Hz, 2 H), 1.83 (m, 1 H), 1.74 (ddd, *J* = 13.1, 11.1, 9.2 Hz, 1 H), 1.47 (s br, 1 H), 1.30 (m, 7 H), 0.89 (t, *J* = 7.8 Hz, 3 H); ^{13}C ($CDCl_3$) δ 210.9, 144.5, 130.5, 129.8, 128.3, 127.2, 105.6, 89.5, 82.4, 75.7, 63.0, 62.7, 58.2, 40.9, 31.4, 29.2, 27.1, 26.2, 25.5, 22.5, 14.0; IR (neat) 3365 (br), 2043, 1977, 1644 cm^{-1}; HRMS *m/z* 358.1585 [calcd for $C_{20}H_{30}O_2Fe$ (M − 3 CO), *m/z* 358.1590].

Reduction of a mixture of **13a** and **13b** (2.1:1, 3.39 g, 7.70 mmol) in the same fashion gave a mixture of **15a** and **15b** (ca. 2:1, 79%). This could be separated by column chromatography (pentane–ether gradient (5:1–7:3)) to afford **15a** (R_f = 0.58, 50%) followed by **15b** (R_f = 0.26, 26%).

(5*R,1′*R**,4′*R**)-Isopropyl Acetal of Tricarbonyl[5-oxo-5-[(1′–4′-η)-pentadeca-1′(*E*),3′(*Z*),6′(*Z*),9′(*Z*)-tetraenyl]pent-2-enal]iron (16a).** To a solution of *rac*-**15a** (1.69 g, 3.82 mmol) in isopropyl alcohol (130 mL) at 0 °C was added *p*-toluenesulfonic acid (130 mg). The mixture was stirred at 0 °C for 24 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic layers were washed with water and brine, dried, and concentrated. The residue was purified by flash chromatography (hexanes–Et_2O (10:1)) to give **16a** as a yellow oil (1.35 g, 73%). Further elution with hexanes/Et_2O (5:1) gave starting material **15a** (0.30 g, 18%). **16a**: ^{1}H NMR ($CDCl_3$) δ 6.00 (dt, *J* = 10.0, 4.2 Hz, 1 H), 5.70 (ddd, *J* = 10.0, 5.3, 2.4 Hz, 1 H), 5.46 (ddd, *J* = 8.7, 5.1, 1.2 Hz, 1 H), 5.38 (m, 1 H), 5.32 (m, 3 H), 5.20 (dd, *J* = 7.6, 5.1 Hz, 1 H), 5.10 (br m, 1 H), 4.09 (hept, *J* = 6.5 Hz, 1 H), 3.63 (q, *J* = 7.4 Hz, 1 H), 2.71 (t, *J* = 6.5 Hz, 1 H), 2.59 (tdd, *J* = 8.2, 5.9, 1.2 Hz, 1 H), 2.26 (dt, *J* = 14.6, 6.4 Hz, 1 H), 2.18 (m, 2 H), 2.10 (t, *J* = 9.1 Hz, 1 H), 2.03 (m, 2 H), 1.92 (m, 1 H), 1.33 (d, *J* = 6.5 Hz, 3 H), 1.26 (m, 7 H), 1.20 (d, *J* = 6.5 Hz, 3 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.1, 131.3, 130.6, 128.6, 128.3, 127.2, 125.7, 93.4, 93.2, 83.8, 70.0, 69.4, 62.2, 59.7, 31.8, 31.4, 29.2, 27.2, 26.4, 25.6, 24.0, 22.5, 21.9, 14.0; IR (CH_2Cl_2) 2046, 1967 cm^{-1}; HRMS *m/z* 400.2071 [calcd for $C_{23}H_{36}O_2Fe$ (M − 3 CO), *m/z* 400.2058].

(5*S,1′*R**,4′*R**)-Isopropyl acetal of tricarbonyl[5-oxo-5-[(1′–4′-η)-pentadeca-1′(*E*),3(*Z*)′,6(*Z*)′,9(*Z*)′-tetraenyl]penta-2(*Z*)-enal]iron (16b)** was prepared from **15b** in a fashion similar to the rearrangement of **15a** to **16a**. The mixture was stirred for 34 h at 0–5 °C. Purification of the crude product by flash chromatography (hexanes–Et_2O (10:1)) gave **16b** as a yellow oil (110 mg, 77%). Further elution (hexanes/Et_2O (10:3)) gave starting material **15b** (12 mg, 10%). **16b**: ^{1}H NMR ($CDCl_3$) δ 5.98 (m, 1 H), 5.68 (ddd, *J* = 10.5, 4.2, 2.9 Hz, 1 H), 5.50 (dd, *J* = 8.8, 4.9 Hz, 1 H), 5.38 (m, 1 H), 5.31 (m, 3 H), 5.15 (dd, *J* = 7.6, 5.4 Hz, 1 H), 5.10 (br s, HW = 12, 1 H), 4.11 (sept, *J* = 6.1 Hz, 1 H), 4.00 (dt, *J* = 9.8, 4.9 Hz, 1 H), 2.69 (t, *J* = 5.9 Hz, 1 H), 2.50 (ddt, *J* = 9.6, 1.2, 6.9 Hz, 1 H), 2.30 (ddd, *J* = 14.9, 9.4, 5.9 Hz, 1 H), 2.21 (m, 1 H), 2.15 (m, 2 H), 2.03 (br q, *J* = 7.1 Hz, 2 H), 1.92 (m, 1 H), 1.29 (m, 10 H), 1.20 (d, *J* = 6.1 Hz, 3 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.0, 131.2, 130.5, 129.9, 127.7, 127.2, 126.2, 92.0, 89.2, 81.6, 68.9, 67.5, 65.8, 58.2, 33.4, 31.4, 29.2, 27.1, 26.3, 25.9, 23.6, 22.5, 21.7, 14.0; IR (neat) 2046, 1969 cm^{-1}; HRMS *m/z* 400.2050 [calcd for $C_{23}H_{36}O_2Fe$ (M − 3 CO), *m/z* 400.2058].

(5*R,1′*R**,4′*R**)-Hemiacetal of Tricarbonyl[5-oxo-5-[(1′–4′-η)-pentadeca-1′(*E*),3′(*Z*),6′(*Z*),9′(*Z*)-tetraenyl]pent-2-enal]iron (17a).** To a solution of *rac*-**16a** (240 mg, 0.50 mmol) in acetone (35 mL) at rt was added 0.05 M H_2SO_4 (3.5 mL), and the solution was stirred for 5 h. Saturated aqueous $NaHCO_3$ (8 mL) was added, and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried and concentrated. Purification of the residue by column chromatography gave the starting material **16a** (12 mg, 5%, eluted with hexanes–Et_2O (5:1)) and **17a** as a yellow oil (173 mg, 79%, eluted with hexanes–Et_2O (5:2)). **17a**: ^{1}H NMR ($CDCl_3$) δ 6.03 (dt, *J* = 9.0, 4.5 Hz, 1 H), 5.79 (ddd, *J* = 10.1, 4.5, 1.7 Hz, 1 H), 5.55 (ddd, *J* = 8.8, 5.1, 1.5 Hz, 1 H), 5.42 (m, 1 H), 5.30 (m, 4 H), 5.20 (dd, *J* = 7.6, 5.1 Hz, 1 H), 3.75 (q, *J* = 7.4 Hz, 1 H), 2.78 (m, 1 H), 2.69 (t, *J* = 6.6 Hz, 1 H), 2.58 (tdd, *J* = 7.8, 5.9, 1.2 Hz, 1 H), 2.25 (dt, *J* = 14.6, 6.6 Hz, 1 H), 2.16 (m, 3 H), 2.03 (br q, *J* = 6.6 Hz, 2 H), 1.88 (m, 1 H), 1.29 (m, 7 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.8, 130.5, 129.6, 128.8, 128.5, 127.1, 125.8, 92.5, 89.5, 83.6, 69.6, 61.8, 59.5, 31.9, 31.4, 29.2, 27.1, 26.3, 25.5, 22.5, 14.0; IR (neat) 3405 (br), 2057, 1998, 1657 cm^{-1}; HRMS *m/z* 358.1589 [calcd for $C_{20}H_{30}O_2Fe$ (M − 3 CO), *m/z* 358.1590].

(5*S,1′*R**,4′*R**)-Hemiacetal of Tricarbonyl[5-oxo-5-[(1′–4′-η)-pentadeca-1′(*E*),3′(*Z*),6′(*Z*),9′(*Z*)-tetraenyl]pent-2*Z*-enal]iron (17b).** To a solution of **16b** (100 mg, 0.21 mmol) in acetone (15 mL) was added 0.05 M H_2SO_4 (1.5 mL) at rt. The mixture was stirred for 4 h and worked up as before. Purification of the crude product by flash chromatography gave starting material **16b** (15 mg, 15%, eluted with hexanes–Et_2O (10:1)) followed by **17b** (75 mg, 82%, eluted with hexanes–Et_2O (5:1)). **17b**: ^{1}H NMR ($CDCl_3$) δ 6.01 (m, 1 H), 5.79 (ddd, *J* = 10.7, 5.0, 2.5 Hz, 1 H), 5.42 (m, 4 H), 5.31 (m, 2 H), 5.18 (dd, *J* = 7.8, 5.4 Hz, 1 H), 3.86 (br q, *J* = 7.0 Hz, 1 H), 2.84 (br s, 1 H), 2.69 (t, *J* = 6.0 Hz, 1 H), 2.52 (ddt, *J* = 13.2, 1.2, 4.5 Hz, 1 H), 2.27 (t, *J* = 8.2 Hz, 2 H), 2.18 (m, 2 H), 2.02 (br q, *J* = 7.1 Hz, 2 H), 1.84 (m, 1 H), 1.29 (m, 7 H), 0.89 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.0, 130.5, 129.9, 128.3, 128.1, 127.2, 126.1, 90.4, 89.1, 82.4, 68.7, 64.5, 58.3, 33.3, 31.4, 29.2, 27.2, 26.2, 25.5, 22.5, 14.0; IR (neat) 3410 (br), 2040, 1956 cm^{-1}; HRMS *m/z* 358.1606 [calcd for $C_{20}H_{30}O_2Fe$ (M − 3 CO), *m/z* 358.1590].

(5*R,6*R**,9*R**)-Lactone of Tricarbonyl[5-hydroxy-(6–9-η)-eicosa-2(*Z*),6(*E*),8(*Z*),11(*Z*),14(*Z*)-pentaenoic acid]iron (18a).** Method A. To a solution of *rac*-**17a** (595 mg, 0.89 mmol) in acetone (30 mL) was added activated MnO_2 (19.7 g). The mixture was stirred for 15 min and filtered through filter-aid, the filter bed washed with acetone, and the solvent evaporated. The residue was purified by flash chromatography (hexanes–Et_2O (5:2)) to give **18a** as a yellow oil (315 mg, 80%).

Method B. To a solution of *rac*-**17a** (120 mg, 0.27 mmol) and pyridinium dichromate (200 mg, 0.54 mmol) in CH_2Cl_2 (10 mL) was added freshly activated 3Å molecular sieve powder (220 mg)

and glacial acetic acid (2 drops). The mixture was stirred for 5 h and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed successively with diluted aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated. The residue was purified by column chromatography to give **18a** (40 mg, 24%, eluted with hexanes–Et_2O (5:1)) followed by what was subsequently identified as the decomplexed product **19** (vide infra) (18 mg, 22%, eluted with hexanes–Et_2O (10:3)).

18a: ^1H NMR ($CDCl_3$) δ 6.89 (dt, J = 9.5, 4.5 Hz, 1 H), 6.04 (d, J = 9.5 Hz, 1 H), 5.58 (dd, J = 8.5, 5.5 Hz, 1 H), 5.33 (m, 4 H), 5.23 (dd, J = 7.4, 5.5 Hz, 1 H), 4.12 (td, J = 9.6, 5.8 Hz, 1 H), 2.69 (t, J = 5.9 Hz, 2 H), 2.53 (m, 2 H), 2.25 (td, J = 14.5, 7.1 Hz, 1 H), 2.12 (t, J = 8.9 Hz, 1 H), 2.02 (br q, J = 7.0 Hz, 2 H), 1.91 (m, 1 H), 1.29 (m, 7 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.1, 163.6, 144.8, 130.7, 129.1, 128.9, 127.0, 121.2, 92.9, 84.6, 81.6, 60.6, 57.6, 31.4, 30.6, 29.2, 27.2, 26.3, 25.5, 22.5, 14.0; IR (neat) 2255, 2051, 1988, 1723 cm^{-1}; HRMS m/z 356.1438 [calcd for $C_{20}H_{28}O_2Fe$ (M – 3 CO), m/z 356.1434].

(5*S,6*R**,9*R**)-Lactone of Tricarbonyl[5-hydroxy-(6–9-η)-eicosa-2(*Z*),6(*E*),8(*Z*),11(*Z*),14(*Z*)-pentaenoic acid]iron (18b).** To a solution of **17b** (40 mg, 0.9 mmol) in acetone (8 mL) was added activated MnO_2 (1.72 g) at rt with vigorous stirring. After 1.5 h, the mixture was filtered through Celite and washed with acetone (4 × 10 mL). The solvent was evaporated, and the residue was purified by column chromatography (hexanes–ethyl acetate (10:1)) to give **17b** as a yellow oil (10 mg, 25%): ^1H NMR ($CDCl_3$) δ 6.89 (ddd, J = 9.8, 6.5, 2.8 Hz, 1 H), 6.04 (ddd, J = 9.8, 2.6, 1.2 Hz, 1 H), 5.58 (ddd, J = 8.9, 4.8, 0.8 Hz, 1 H), 5.34 (m, 4 H), 5.21 (m, 1 H), 4.50 (pent, J = 5.3 Hz, 1 H), 2.69 (t, J = 6.2 Hz, 1 H), 2.59 (ddd, J = 9.5, 5.6, 1.2 Hz, 1 H), 2.54 (m, 2 H), 2.22 (m, 2 H), 2.03 (br q, J = 6.8 Hz, 2 H), 1.83 (ddd, J = 14.3, 9.5, 5.0 Hz, 1 H), 1.29 (m, 7 H), 0.89 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.2, 163.3, 144.3, 130.7, 129.6, 128.6, 127.1, 121.7, 89.1, 82.9, 78.8, 60.6, 58.5, 32.6, 31.5, 29.2, 27.2, 26.2, 25.6, 22.5, 14.0; IR (CH_2Cl_2) 2051, 1991, 1723 cm^{-1}; HRMS m/z 384.1386 [calcd for $C_{21}H_{28}O_3Fe$ (M – 2 CO), m/z 384.1383].

(5*R,6*R**,9*R**)-Lactone of Tricarbonyl[5-hydroxy-(6–9-η)-eicosa-6(*E*),8(*Z*),11(*Z*),14(*Z*)-tetraenoic acid]iron (20a). Method A.** A mixture of $Fe(CO)_5$ (489 mg, 2.50 mmol) and DABCO (140 mg, 1.25 mmol) in DMF–H_2O (98:2 v/v, 3.5 mL) was flushed with N_2 and stirred for 10 min at room temperature. The mixture was transferred, by cannula, to a flask containing *rac*-**18a** (55 mg, 0.13 mmol) and stirred for 50 h. The mixture was added to H_2O (2 mL) and extracted with Et_2O (3 × 30 mL). The combined extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was purified by flash chromatography (hexanes–ethyl acetate (5:1)) to give **20a** as a yellow oil (20 mg, 36%) and starting material **18a** (10 mg, 2%).

Method B. To a solution of $[(Ph_3P)CuH]_6$ (178 mg, 0.09 mmol) in moistened benzene (10 mL, deoxygenated by N_2 for 10 min) was added *rac*-**18a** (80 mg, 0.18 mmol). The mixture was stirred for 20 min and then opened to air and stirred for 1 h, during which time copper-containing decomposition products precipitated. The crude mixture was concentrated nearly to dryness and passed through a column using CH_2Cl_2 as eluant. The product fractions were concentrated, and the residue was purified by flash chromatography (hexanes–ethyl acetate (5:1)) to give **20a** as a yellow oil (28 mg, 31%).

20a: ^1H NMR ($CDCl_3$) δ 5.54 (dd, J = 7.6, 5.2 Hz, 1 H), 5.26–5.42 (m, 4 H), 5.21 (dd, J = 8.3, 5.2 Hz, 1 H), 3.99 (td, J = 10.1, 3.5 Hz, 1 H), 2.70 (t, J = 6.8 Hz, 2 H), 2.62 (m, 1 H), 2.59 (dt, J = 17.6, 6.0 Hz, 1 H), 2.42 (ddd, J = 17.6, 9.0, 7.1 Hz, 1 H), 2.26 (dt, J = 14.9, 7.1 Hz, 1 H), 2.16–1.65 (m, 7 H), 1.26–1.38 (m, 7 H), 0.88 (t, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.4, 170.9, 130.7, 129.2, 128.9, 127.0, 92.9, 84.7, 84.5, 60.5, 59.1, 31.5, 29.4, 29.2, 29.1, 27.1, 26.4, 25.5, 22.5, 18.9, 14.0; IR (CH_2Cl_2) 2043, 1962, 1734 cm^{-1}; HRMS m/z 358.1595 [calcd for $C_{20}H_{30}O_2Fe$ (M – 3 CO), m/z 358.1590].

(5*S,6*R**,9*R**)-Lactone of Tricarbonyl[5-hydroxy-(6–9-η)-eicosa-6(*E*),8(*Z*),11(*Z*),14(*Z*)-tetraenoic acid]iron (20b).** The reduction of **18b** with $[(Ph_3P)CuH]_6$ was performed in the same fashion as for the reduction of **18a**. Purification of the crude product by flash chromatography gave lactone **20b** as a yellow oil in 33% yield: ^1H NMR ($CDCl_3$) δ 5.58 (dd, J = 8.7, 5.2 Hz, 1 H), 5.27–5.42 (m, 4 H), 5.20 (dd, J = 7.6, 5.2 Hz, 1 H), 4.44 (ddd, J = 11.0, 5.3, 3.2 Hz, 1 H), 2.69 (t, J = 6.8 Hz, 2 H), 2.58 (m, 2 H), 2.47 (ddd, J = 17.6, 9.9, 7.4 Hz, 1 H), 2.20–1.80 (m, 8 H), 1.26–1.37 (m, 7 H), 0.89 (t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.4, 170.4, 130.6, 129.6, 128.5, 127.1, 88.8, 82.6, 80.8, 62.3, 58.4, 31.6, 31.5, 29.5, 29.2, 27.2, 26.2, 25.5, 22.5, 18.9, 14.0; IR ($CDCl_3$) 2049, 1969, 1734 cm^{-1}; HRMS m/z 358.1610 [calcd for $C_{20}H_{30}O_2Fe$ (M – 3 CO), m/z 358.1590].

Methyl 5-Hydroxyeicosa-6(*E*),8(*Z*),11(*Z*),14(*Z*)-tetraenoate (5-HETE Methyl Ester). From Lactone 20a. To a solution of *rac*-**20a** (50 mg, 0.15 mmol) in methanol (5 mL) at –10 °C was added in one portion, with stirring, $(NH_4)_2Ce(NO_2)_6$ (219 mg, 0.4 mmol). After 20 min H_2O (2 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with H_2O and brine, dried, and concentrated. The residue was dried in vacuo to give *rac*-**1** as a light yellow oil (30 mg, 79%): ^1H NMR ($CDCl_3$) δ 6.53 (dd, J = 15.1, 11.0 Hz, 1 H), 6.00 (t, J = 11.0 Hz, 1 H), 5.69 (dd, J = 15.1, 6.6 Hz, 1 H), 5.33–5.43 (m, 5 H), 4.19 (q, J = 6.6 Hz, 1 H), 3.67 (s, 3 H), 2.96 (t, J = 6.3 Hz, 2 H), 2.82 (t, J = 6.2 Hz, 2 H), 2.36 (t, J = 7.2 Hz, 2 H), 2.05 (q, J = 6.6 Hz, 2 H), 1.54–1.79 (m, 5 H), 1.22–1.40 (m, 6 H), 0.89 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.9, 135.9, 130.6, 130.5, 128.9, 127.8, 127.4, 127.3, 125.7, 72.2, 51.4, 36.6, 33.8, 31.4, 29.2, 27.2, 26.0, 25.6, 22.5, 20.8, 14.0; IR ($CDCl_3$) 3609, 1721 cm^{-1}. The ^1H and ^{13}C NMR spectra obtained are identical with those of authentic 5-HETE methyl ester provided by Dr. Zamboni (Merck-Frosst).

From Lactone 20b. The procedure was the same as above and gave pure 5-HETE methyl ester in 88% yield.

Lactone of 5-hydroxyeicosa-2*Z*,6*E*,8*Z*,11*Z*,14*Z*-pentaenoic acid (19) was prepared from *rac*-**18a** by decomplexation in a fashion similar to the decomplexation of **20a**. Workup afforded **19** as a light yellow oil in quantitative yield: ^1H NMR ($CDCl_3$) δ 6.89 (dt, J = 9.6, 4.2 Hz, 1 H), 6.66 (dd, J = 15.1, 11.0 Hz, 1 H), 6.04 (dt, J = 9.6, 1.7 Hz, 1 H), 5.99 (t, J = 11.0 Hz, 1 H), 5.74 (dd, J = 15.1, 6.6 Hz, 1 H), 5.49 (dt, J = 11.0, 7.3 Hz, 1 H), 5.27–5.44 (m, 4 H), 4.98 (q, J = 6.6 Hz, 1 H), 2.95 (t, J = 7.3 Hz, 2 H), 2.79 (t, J = 6.7 Hz, 2 H), 2.45 (ddd, J = 6.6, 4.2, 1.7 Hz, 2 H), 2.03 (q, J = 6.7 Hz, 2 H), 1.24–1.37 (m, 6 H), 0.86 (t, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.9, 144.6, 132.5, 130.5, 129.1, 129.0, 128.2, 127.2, 127.1, 126.8, 121.4, 77.8, 31.4, 29.8, 29.2, 27.1, 26.0, 25.5, 22.4, 14.0; IR ($CDCl_3$) 1721 cm^{-1}; GC/MS 300 (M^+, 7), 229 (3), 215 (11), 189 (4), 163 (2), 145 (15), 131 (25), 117 (45), 105 (28), 97 (45), 91 (70), 79 (47), 77 (27), 69 (40), 55 (29), 43 (28), 41 (100); HRMS m/z 300.2083 [calcd for $C_{20}H_{28}O_2$, m/z 300.2082].

Lactone of 5-Hydroxyeicosa-6*E*,8*Z*,11*Z*,14*Z*-tetraenoic Acid (5-HETE Lactone). The reduction of **19** with $[PPh_3CuH]_6$ was performed in a fashion similar to the reduction of **18a**. Purification by flash chromatography (hexanes–ethyl acetate (10:1)) gave 5-HETE lactone as a light yellow oil in 19% yield: ^1H NMR ($CDCl_3$) δ 6.61 (ddt, J = 15.3, 11.1, 1.2 Hz, 1 H), 6.00 (t, J = 11.1 Hz, 1 H), 5.69 (dd, J = 15.3, 6.4 Hz, 1 H), 5.48 (dd, J = 11.1, 7.2 Hz, 1 H), 5.28–5.43 (m, 4 H), 4.88 (dddd, J = 6.4, 6.3, 3.3, 1.0 Hz, 1 H), 2.96 (t, J = 7.2 Hz, 2 H), 2.81 (t, J = 6.0 Hz, 2 H), 2.43–2.66 (m, 2 H), 2.05 (q, J = 6.9 Hz, 2 H), 1.82–2.00 (m, 2 H), 1.63–1.74 (m, 2 H), 1.26–1.37 (m, 6 H), 0.88 (t, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.1, 132.1, 130.6, 129.2, 127.3 (3 C), 127.0, 80.3, 31.5, 29.5, 28.4, 27.2, 26.1, 25.6, 22.6, 18.3, 14.1; IR ($CDCl_3$) 1731, 1242, 1035 cm^{-1}; GC/MS 302 (M^+, 20), 231 (19), 215 (6), 207 (13), 145 (14), 131 (40), 117 (58), 99 (61), 79 (59), 71 (100), 67 (50), 55 (79), 43 (84), 41 (96). The ^1H NMR spectra data obtained was identical to the literature values.[5b]

Tricarbonyl[(5*R,6*R**,9*R**)- and (5*S**,6*R**,9*R**)-(6–9-η)-5-hydroxyeicosa-6(*E*),8(*Z*),11(*Z*),14(*Z*)-tetraenoate]iron (*rac*-22a and *rac*-22b).** To a solution of *tert*-butyllithium (1.7 M in pentane, 3.79 mL, 6.44 mmol) at –78 °C was added, via cannula, a solution of **21** (0.81 g, 3.2 mmol) in dry Et_2O (10 mL). The solution was stirred for 15 min, and then $CuBr{\cdot}Me_2S$ (0.22 g, 1.08 mmol) was added in one portion. The mixture was stirred for an additional 20 min, and then a precooled solution of *rac*-**3** (0.27 g, 0.72 mmol) in Et_2O (10 mL) was added dropwise. The mixture was stirred for 40 min, and then saturated aqueous NH_4OH was added. The mixture was warmed to rt, extracted with Et_2O, dried, and concentrated. After evaporation of the solvent, the residue was dissolved in 0.05 M *p*-TsOH in THF–H_2O (15 mL, 9:1) and stirred for 8 min. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3

× 15 mL), and the combined extracts were dried. Evaporation of the solvent gave a residue which was purified by flash chromatography (ethyl acetate) to afford a yellow oil. The oil was dissolved in methanol (8 mL) at rt, and saturated methanolic K_2CO_3 (4 mL) was added. The mixture was stirred for 5 min, neutralized with 1% HCl, extracted with Et_2O, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (pentane–ether gradient (10:3–2:1)) gave *rac*-**22b** (65 mg, 19%) followed by *rac*-**22a** (120 mg, 35%) as yellow oils.

rac-**22b**: R_f 0.79 (pentane–Et_2O (1:1)); ^1H NMR ($CDCl_3$) δ 5.41 (dd, J = 8.2, 5.5 Hz, 1 H), 5.38–5.24 (m, 4 H), 5.18 (dd, J = 7.3, 5.5 Hz, 1 H), 3.67 (s, 3 H), 3.53 (q, J = 6.4 Hz, 1 H), 2.69 (t, J = 6.0 Hz, 1 H), 2.55 (br q, J = 7.3 Hz, 1 H), 2.38 (t, J = 7.3 Hz, 2 H), 2.31–2.20 (m, 2 H), 2.03 (q, J = 6.6 Hz, 2 H), 1.96–1.26 (m, 13 H), 0.89 (t, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.1, 173.9, 130.7, 129.8, 128.5, 127.2, 90.5, 82.3, 74.0, 68.8, 59.1, 51.5, 39.3, 33.7, 31.5, 29.3, 27.2, 26.3, 25.6, 22.5, 21.2, 14.0; IR (neat) 3489 (br), 2042, 1971, 1736 cm^{-1}; HRMS m/z 390.1850 [calcd for $C_{21}H_{34}O_3Fe$ (M – 3 CO), m/z 390.1851].

rac-**22a**: R_f 0.52 (pentane–Et_2O (1:1)); ^1H NMR ($CDCl_3$) δ 5.50 (dd, J = 8.0, 5.1 Hz, 1 H), 5.44–5.24 (m, 4 H), 5.17 (dd, J = 7.7, 5.1 Hz, 1 H), 3.67 (s, 3 H), 3.44 (td, J = 7.7, 1.8 Hz, 1 H), 2.69 (t, J = 6.2 Hz, 1 H), 2.57 (q, J = 8.0 Hz, 1 H), 2.38 (t, J = 7.0 Hz, 2 H), 2.27–1.58 (m, 12 H), 1.29 (m, 6 H), 0.89 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.1, 174.1, 130.7, 129.7, 128.6, 127.2, 92.1, 83.3, 74.6, 65.3, 59.5, 51.5, 37.9, 33.5, 31.5, 29.3, 27.2, 26.5, 25.6, 22.5, 20.7, 14.0; IR (neat) 3435 (br), 2042, 1971, 1738 cm^{-1}; HRMS m/z 390.1935 [calcd for $C_{21}H_{34}O_3Fe$ (M – 3 CO), m/z 390.1851].

Tricarbonyl[(5*R*,6*R*,9*S*)- and (5*S*,6*R*,9*S*)-(6–9-η)-methyl 5-hydroxyeicosa-6*E*,8*Z*,11*Z*,14*Z*-tetraenoate]iron ((5*R*,6*R*)-22a and (5*S*,6*R*)-22b) were prepared from (2*R*)-**3** in the same fashion as the preparation of *rac*-**22a** and *rac*-**22b**. Purification of the residue by flash chromatography (pentane–Et_2O gradient, 10:3–2:1) gave (5*S*,6*R*)-**22b** (0.24 g, 21%) followed by (5*R*,6*R*)-**22a** (0.38 g, 33%) as yellow oils. All the spectral data are identical with those values of the racemic compound.

***rac*-5-HETE methyl ester (*rac*-1)** was prepared by decomplexation of *rac*-**22a** or *rac*-**22b** using $(NH_4)_2Ce(NO_2)_6$ in methanol, in a fashion similar to the decomplexation of **20a**. The spectra were identical with that of authentic 5-HETE methyl ester.

5(*R*)-HETE methyl ester ((–)-1) was prepared by decomplexation of (5*R*,6*R*)-**22a** in the same manner as the racemic 5-HETE using $(NH_4)_2Ce(NO_2)_6$ in methanol. Purification by column chromatography (hexanes–Et_2O (5:2)) gave 5(*R*)-HETE methyl ester (–)-1 as a colorless oil in 86% yield: $[\alpha]_D$ = –13.5° (c = 2.00, benzene).

5(*S*)-HETE methyl ester ((+)-1) was prepared from (5*S*,6*R*)-**22b** in a fashion similar to the decomplexation of (5*R*,6*R*)-**22a**. Purification by column chromatography (hexanes–Et_2O (5:2)) afforded 5(*S*)-HETE methyl ester (+)-1 as a colorless oil in 87% yield. All the spectral data are identical with those values of the racemic compound: $[\alpha]_D$ = +14.2° (c = 2.00, benzene).

MTPA Ester of 5(*R*)-HETE Methyl Ester (23a). A solution of (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (250 mg, 1.08 mmol), *N*,*N*-dicyclohexylcarbodiimide (220 mg, 1.08 mmol), 5(*R*)-HETE methyl ester ((–)-1) (120 mg, 0.36 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (26 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 1.5 h. The reaction was quenched by the addition of H_2O (1 mL) and extracted with Et_2O (3 × 20 mL). The organic layers were washed with 3% HCl (3 × 20 mL), water, and brine, dried, and evaporated. Purification by column chromatography (hexanes–ethyl acetate (10:1)) afforded the known compound **23a**[6b] as a colorless oil (130 mg, 66%): ^1H NMR ($CDCl_3$) δ 7.51 (m, 2 H), 7.39 (m, 3 H), 6.67 (dd, J = 14.7, 10.3 Hz, 1 H), 5.98 (t, J = 10.9 Hz, 1 H), 5.64 (dd, J = 14.8, 7.8 Hz, 1 H), 5.57–5.32 (m, 6 H), 3.65 (s, 3 H), 3.54 (s, 3 H), 2.95 (t, J = 7.0 Hz, 2 H), 2.81 (t, J = 6.5 Hz, 2 H), 2.27 (t, J = 7.1 Hz, 2 H), 2.05 (q, J = 6.8 Hz, 2 H), 1.75–1.66 (m, 2 H), 1.61–1.53 (m, 2 H), 1.37–1.27 (m, 6 H), 0.89 (t, $_J$ = 6.6 Hz, 3 H); ^1H NMR (d_6-acetone) δ 7.53 (m, 2 H), 7.46 (m, 3 H), 6.82 (dd, J = 15.0, 11.1 Hz, 1 H), 6.07 (t, J = 11.1 Hz, 1 H), 5.79 (dd, J = 15.0, 7.7 Hz, 1 H), 5.61 (q, J = 6.6 Hz, 1 H), 5.52 (dt, J = 10.7, 7.7 Hz, 1 H), 5.37 (m, 4 H), 3.60 (s, 3 H), 3.55 (m, 3 H), 3.02 (t, J = 6.0 Hz, 2 H), 2.81 (m, 2 H), 2.29 (t, J = 7.3 Hz, 2 H), 2.08 (t, J = 6.7 Hz, 2 H), 1.73 (m, 2 H), 1.54 (m, 2 H), 1.31 (m, 6 H), 0.87 (t, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.3, 165.8, 132.3, 130.6, 129.5, 129.3, 129.2, 129.1, 128.7, 128.3, 127.4, 127.3, 127.2, 127.0, 125.3, 121.4, 76.8, 55.4, 51.4, 50.0, 33.7, 33.4, 31.4, 29.2, 27.2, 26.1, 25.6, 22.5, 20.5, 14.0; IR (neat) 1743, 1664 cm^{-1}.

MTPA ester of 5(*S*)-HETE methyl ester (23b) was prepared in the same fashion as the MTPA ester of 5(*R*)-HETE methyl ester. The ^1H and ^{13}C NMR spectra of **23b** were identical with those of **23a** in $CDCl_3$: ^1H NMR (d_6-acetone) δ 7.51 (m, 2 H), 7.45 (m, 3 H), 6.68 (dd, J = 14.1, 11.2 Hz, 1 H), 6.01 (t, J = 11.2 Hz, 1 H), 5.61 (m, 2 H), 5.36 (m, 5 H), 3.61 (s, 3 H), 3.57 (m, 3 H), 2.95 (t, J = 6.0 Hz, 2 H), 2.84 (m, 2 H), 2.37 (t, J = 7.3 Hz, 2 H), 2.09 (t, J = 6.8 Hz, 2 H), 1.77 (m, 2 H), 1.69 (m, 2 H), 1.30 (m, 6 H), 0.87 (t, J = 6.7 Hz, 3 H); IR (neat) 1743, 1666 cm^{-1}.

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Supplementary Material Available: ^1H and/or ^{13}C NMR spectra for all new compounds (33 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.