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Synthesis and Reactivity of Acyclic (pentadienyl)iron(1+) Cations: Model Studies for the Preparation of the 8*E*,10*Z*,16*E*,18*E*-Tetraene Segment of Macrolactin A

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Synthesis And Reactivity Of Acyclic (Pentadienyl)Iron(1+) Cations: Model Studies For The Preparation Of The 8*E*,10*Z*,16*E*,18*E*-Tetraene Segment Of Macrolactin A

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Abstract

The dicarbonyl(1,2-dimethylpentadienyl)triphenylphosphineiron(1+) cation (**11**) has been prepared from methyl 4-methyl-2*E*,4*E*-hexadienoate in four steps. The cation (**11**) reacts with hydride and carbon nucleophiles in a regiospecific fashion to afford (3-methyl-2*E*,4*Z*-diene)iron complexes. Dicarbonyl(3-methyl-7-nitro-2*E*,4*Z*-

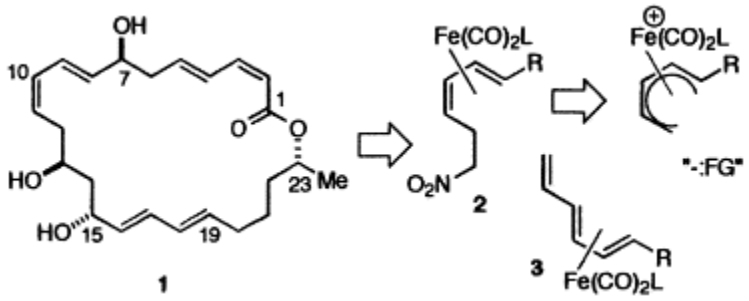
heptadiene)triphenylphosphineiron (**15**), the product from the reaction of **11** with nitromethane anion, has been utilized as a precursor for nitrile oxide–olefin cyclocondensations.

Keywords

(1,3-Diene)iron complexes, Bis-iron tetraene complexes, Nitrile oxide–olefin cycloadditions, Isoxazolines

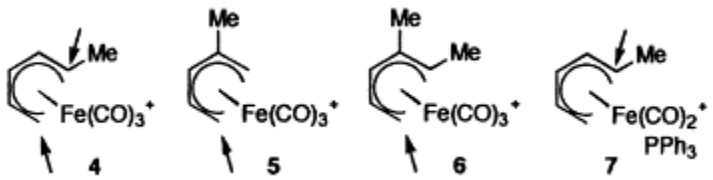
1. Introduction

Macrolactin A (**1**) is a 24-membered polyene macrolide isolated from a taxonomically-undefined deep sea bacterium [1a]. This compound exhibits antiviral activity against Herpes Simplex I and II and against HIV. Unfortunately, the culturing of this bacterium has been 'unreliable' [1b]. The structure of **1** was assigned on the basis of NMR spectroscopy [1a], and by chemical degradation and synthesis of the fragments [1b]. Recently total syntheses by Smith and Ott [2a] and by Carreira's group [2b] have corroborated the structural assignment. These syntheses, as well as work by Boyce and Pattenden [2c]and by Rychnovsky and Pickering [2d] have utilized Pd-coupling methodology for construction of the diene linkages. We have previously reported on a fundamentally different strategy for the preparation of the C11–C24 segment of **1** which relies on the ability of an $Fe(CO)_3$ adjunct to control the introduction of the remote asymmetric centers at C15 and C23 [3]. We [3], [4] and others [5] have demonstrated that intermolecular nitrile oxide–(triene)$Fe(CO)_3$ cyclocondensation methodology can be utilized for the diastereoselective introduction of an asymmetric center adjacent to a complexed diene. In conformity to this strategy, disconnection of **1** at the *anti*-1,3-diol functionality generates a nitro-diene fragment **2** and a triene fragment **3** (Scheme 1). Furthermore, the 8*E*,10*Z*-diene segment **2** might be generated via nucleophilic addition to a (pentadienyl)iron cation.



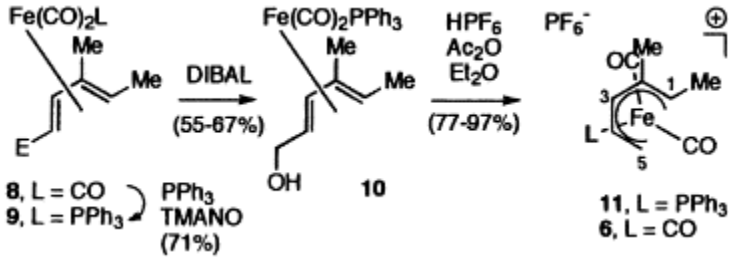
Scheme 1.

We have previously prepared the substituted (pentadienyl)iron cations **4**–**7** [6]. Nucleophilic attack on these cations, at the terminal positions, occurs with regioselectivity as indicated by the arrows. In these studies, we found that substitution of a carbonyl ligand by triphenylphosphine resulted in improved regioselectivity (cf. **4** versus **7**). Herein, we report on the preparation and reactivity of dicarbonyl(1,2-dimethylpentadienyl)triphenylphosphineiron(1+) cation (**11**) (the $Fe(CO)_2PPh_3$ ligated analog of **6**) and the application of products from these reactions in the model studies for the preparation of the 8*E*,10*Z*,16*E*,18*E*-tetraene segment of macrolactin A.



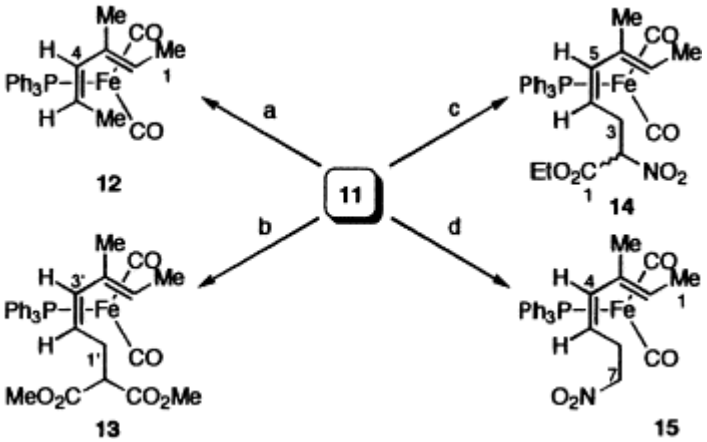
2. Results and discussion[3]

Ligand substitution [7] of (methyl 4-methyl-2,4-hexadienoate)$Fe(CO)_3$ (**8**) gave the $Fe(CO)_2PPh_3$ ligated complex **9** in good isolated yield (Scheme 2). Reduction of **9** gave the dienol complex **10**. Protic dehydration of **10** gave the (1,2-dimethylpentadienyl)$Fe(CO)_2PPh_3^+$ cation (**11**) in excellent yield (Scheme 2). Cation **11** was assigned a cisoid geometry on the basis of its ^{1}H NMR spectral data. In particular, the coupling between H-3 and H-4 (7.2 Hz) is characteristic of a cisoid relationship between these two protons. We [6a] and others [7] have reported that for (1-substituted pentadienyl)$Fe(CO)_2PPh_3^+$ cations, the bulky triphenylphosphine ligand occupies the basal site opposite to the C1 substituent. This also appears to be the case for **11**; notably, the chemical shifts for H-4 and H-5_{exo} of **11** are approximately 1.0 and 1.3 ppm upfield of those for the corresponding $Fe(CO)_3$ligated cation **6** [6b] while the signal for H-1 of **11** is shifted upfield only 0.2 ppm compared to the same signal for **6**. The greater upfield shifts for H-4 and H-5_{exo} may be attributed to the anisotropic effect of the aryl groups of the triphenylphosphine ligand.



Scheme 2.

The reaction of **11** with sodium cyanoborohydride gave the *E*,*Z*-diene complex **12** resulting from nucleophilic attack at C5 (Scheme 3). The structure of **12** was assigned on the basis of its ^{1}H NMR spectral data. In particular, the ^{1}H NMR spectrum of **12** exhibits three signals at δ 2.02 (s), 1.45 (d) and 1.06 (d) ppm corresponding to the three methyl groups. The doublet at δ 3.68, corresponding to H-4, is shifted considerably upfield as compared to the corresponding signal for the $Fe(CO)_3$ ligated complex (δ 5.09 ppm) [6b]. This upfield shift may be attributed to the anisotropic effects of the triphenylphosphine ligand situated in the basal position of complex **12**.

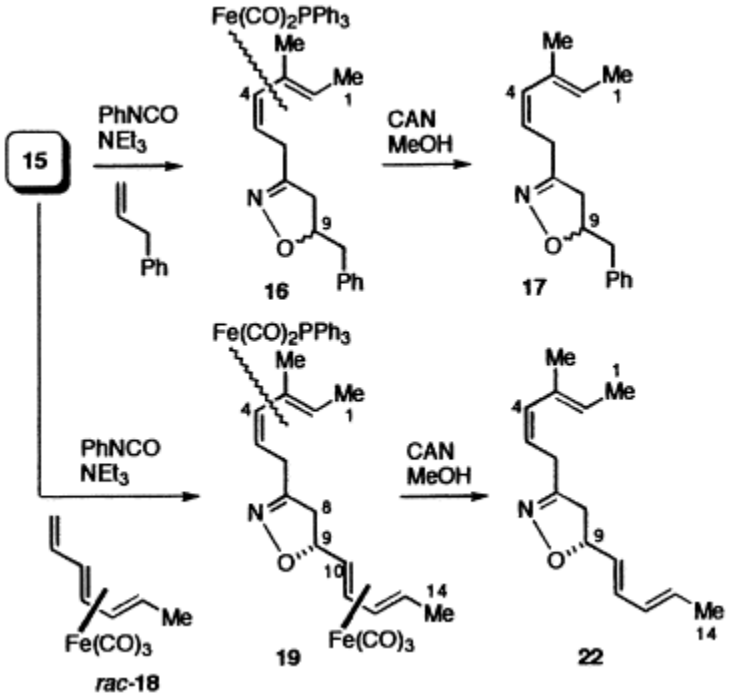


Scheme 3.

Reaction of **11** with lithium dimethyl malonate or lithium ethyl nitroacetate gave the *E*,*Z*-diene complexes **13** or **14**, respectively. The structures of **13** and **14** were assigned by comparison of their ^{1}H NMR spectral data with that of **12**. Complex **14** is produced as a 1:1 mixture of diastereomers at C2. Finally, reaction of **11** with the anion derived from the deprotonation of nitromethane with n-butyl lithium gave the 1° nitro diene complex **15**. The structure of **15** was assigned on the basis of its ^{1}H NMR spectral data. In particular, the

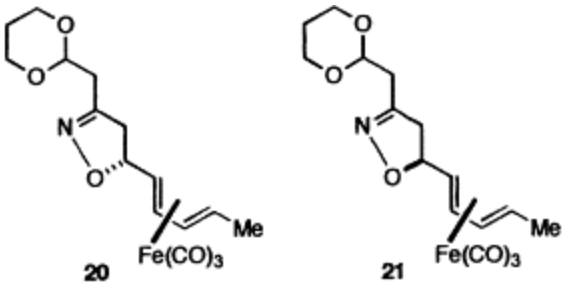
appearance of the signal for H-4 as a doublet at δ 3.82 was indicative of the 3-methyl-2*E*,4*Z*-pentadienyl fragment, while coupling between the H-7 and H-6 protons indicated the formation of the C□C bond between carbons 6 and 7. While O-alkylation is frequently encountered for nitroalkane monoanions [8], C-alkylation has been previously demonstrated using tricarbonyl(cyclohexadienyl)iron(1+) cations as the electrophile [9]. From these results, cation **11** was found to react with nucleophiles in a regioselective fashion and the regioselectivity is the same as that observed for cation **6**.

Generation of the nitrile oxide derived from the 1° nitro complex **15** (PhNCO/NEt_3) [10] in the presence of allylbenzene gave the isoxazoline **16** (Scheme 4). The signals for H-4 appear as two doublets in the ^{1}H NMR spectrum of **16** (δ 3.78 and 3.75 ppm), indicating the formation of a 1:1 mixture of diastereomers at C-9. Thus the diene–iron functionality present in **15** does not exert any facial preference for 1,3-dipolar cycloaddition to allylbenzene. This is not surprising since the diastereoselectivity of nitrile oxide–olefin cycloadditions are little influenced by the presence of an α-asymmetric center in the nitrile oxide component [11]. Oxidative decomplexation of **16** gave the dienyl isoxazoline **17**.



Scheme 4.

Similarly, reaction of the nitrile oxide derived from *rac*-**15** under Mukaiyama conditions with the triene–iron complex *rac*-**18** gave the bimetallic tetraene isoxazoline **19** (Scheme 4). While four sets of racemic diastereomers are possible, examination of the NMR spectra of **19** indicated the presence of only two diastereomers. The *ψ-exo* relative stereochemistry of the C8–C14 segment was assigned by comparison of the ^{13}C NMR chemical shifts for C-8, C-9, and C-10 with those of the known *ψ-exo* and *ψ-endo* dienylisoxazoline complexes **20** and **21** [4a]. In particular, the diastereomeric signals for **19**(approximately δ 44, 84 and 60 ppm) more closely match those of **20** (δ 45.0, 83.6 and 59.4 ppm) than those of **21** (δ 48.0, 85.5 and 63.1 ppm). Thus, the (tricarbonyl)iron adjunct of **18** controls the diastereoselectivity of the cyclocondensation as has been observed in other cases [4], [5]. Finally, oxidative decomplexation of **19** afforded the bis-dienyl isoxazoline **22** (Scheme 4). The stereochemical assignment for **22** was based upon the magnitude of olefinic vicinal proton coupling constants observed.



In summary, a methodology for the preparation of the 8*E*,10*Z*,16*E*,18*E* tetraene segment of macrolactin A has been developed. Application of this methodology to the asymmetric synthesis of **1** is in progress.

3. Experimental

3.1. General data

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. All melting point measurements were carried out on a Mel-Temp apparatus and are uncorrected. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively using a GE Omega GN-300 spectrometer. Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN. High resolution mass spectra were performed at Washington University Resource for Biomedical and Bio-organic Mass Spectrometry. Dry tetrahydrofuran (THF) and dry ether were distilled from potassium and sodium benzophenone ketyl, respectively. Anhydrous hexanes were purchased from Aldrich Chemical. All other solvents were spectral grade and were used without further purification. Tricarbonyl(1,3*E*,5*E*-heptatriene)iron (**18**) was prepared by the literature procedure [4b].

3.2. Tricarbonyl(methyl 4-methyl-2*E*,4*E*-hexadienoate)iron (8)

To a solution of methyl 4-methyl-2*E*,4*E*-hexadienoate (3.00 g, 21.4 mmol) in benzene (120 ml) was added solid $Fe_2(CO)_9$ (11.7 g, 32.1 mmol). The mixture was stirred at r.t. for 1 h, and then heated at reflux for 10 h. The reaction mixture was cooled, additional $Fe_2(CO)_9$ (3.9 g, 10.7 mmol) was added, and the mixture was heated at reflux for an additional 5 h. The mixture was cooled, filtered through filter-aid, and the filter bed was washed with CH_2Cl_2. The combined organic phases were concentrated and the residue purified by column chromatography (SiO_2, hexanes–ethyl acetate (10:1)) to afford **8** as a yellow solid (4.43 g, 74%). *Anal.* Calc. for $C_{11}H_{12}O_5Fe$: C, 47.35; H, 3.97. Found: C, 47.56; H, 4.13%. ^{1}H NMR ($CDCl_3$): δ 5.68 (d, *J*=7.8 Hz, H-3), 3.64 (s, OMe), 2.16 (s, Me-4), 1.47 (d, *J*=6.3 Hz, Me-6), 1.29 (q, *J*=6.3 Hz, H-5), 0.85 (d, *J*=7.8 Hz, H-2). $^{13}C\{^{1}H\}$ ($CDCl_3$): δ 173.3 (C-1), 102.7 (C-4), 83.5 (C-3), 59.3 (C-5), 51.4 (OMe), 42.7 (C-2), 17.8 (Me-4), 15.8 (Me-6).

3.3. Dicarbonyl(methyl 4-methyl-2*E*,4*E*-hexadienoate)triphenylphosphineiron (9)

A mixture of tricarbonyl(methyl 4-methyl-2*E*,4*E*-hexadienoate)iron (4.43 g, 15.8 mmol) and triphenylphosphine (4.91 g, 17.4 mmol) in acetone (75 ml) was heated at reflux for 2 h. Solid trimethylamine *N*-oxide (3.52 g, 31.7 mmol) was added and the mixture was heated at reflux for an additional 1 h. The reaction mixture was cooled and extracted with ether. The combined extracts were dried and concentrated. The residue was purified by column chromatography (SiO_2, 3:1 hexanes–ethyl acetate) to afford **9** as a yellow solid (5.46 g, 67%). *Anal.* Calc. for $C_{28}H_{27}O_4PFe$: C, 65.39; H, 5.29. Found: C, 65.34; H, 5.34%. M.p. 156–158°C. ^{1}H NMR ($CDCl_3$): δ 7.6–7.4 (m, Ar*H*), 5.64 (br m, H-3), 3.24 (s, OMe), 2.09 (s, Me-4), 1.12 (d, *J*=6.3 Hz, Me-6), −0.30 (br m, H-2 and H-5). $^{13}C\{^{1}H\}$ ($CDCl_3$): δ 174.6 (C-1), 135.7 (d, $J_{P□}$=38.8 Hz, Ar*C*), 132.8 (d, $J_{P□}$=10.9 Hz, Ar*C*), 129.4 (Ar*C*), 128.1 (d, $J_{P□}$=9.7, Ar*C*), 101.7 (C-4), 84.5 (C-3), 61.8 (C-5), 50.6 (OMe), 45.7 (C-2), 18.4 (Me-4), 15.0 (Me-6).

3.4. Dicarbonyl(4-methyl-2*E*,4*E*-hexadien-1-ol)triphenylphosphineiron (10)

To a solution of **9** (3.79 g, 7.37 mmol) in anhydrous hexanes (45 ml), cooled to −30°C, was added a solution of DIBAL in hexanes (15 ml, 1.0 M, 15 mmol). The reaction mixture was stirred at this temperature for 90 min, and

then methanol (20 ml) was cautiously added. The mixture was diluted with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined extracts were washed with brine, dried and the solvent evaporated. The residue was purified by column chromatography (SiO_2, 3:1 hexanes–ethyl acetate) to afford **10** as a yellow solid (1.96 g, 56%). *Anal.* Calc. for $C_{27}H_{27}O_3PFe$: C, 66.68; H, 5.60. Found: C, 66.30; H, 5.41%. M.p. 128–130°C. ^{1}H NMR ($CDCl_3$): δ 7.56–7.36 (m, Ar*H*), 4.99 (d, *J*=6.9 Hz, H-3), 3.38 (br t, H-1), 3.26 (dd, *J*=4.3, 11.5 Hz, H-1′), 2.10 (s, Me-4), 1.03 (d, *J*=6.3 Hz, Me-6), 1.00 (br s, OH), −0.38 (m, H-2 and H-5). ^{13}C{^{1}H} ($CDCl_3$): δ 136.4 ($J_{P□}$=37.5 Hz, Ar*C*), 132.6 ($J_{P□}$=10.9 Hz, Ar*C*), 129.3 (Ar*C*), 128.2 ($J_{P□}$=8.5 Hz, Ar*C*), 101.1(C-4), 85.4 (C-3), 65.9 (C-1), 60.5 (C-5), 58.4 (C-2), 18.4 (Me-4), 15.2 (Me-6).

3.5. Dicarbonyl(1,2-dimethylpentadienyl)triphenylphosphineiron(1+) hexafluorophosphate (11)

To a solution of **10** (2.35 g, 4.85 mmol) in Ac_2O (6.5 ml) at 0°C was added dropwise a cold solution of HPF_6 (4 ml, 60% solution) in Ac_2O (2.5 ml). The mixture was stirred for 30 min, during which time a bright-yellow precipitate formed. The mixture was added to a large excess of Et_2O (600 ml). The ether was decanted and the precipitate dissolved in a minimal amount of CH_3NO_2 (1.5 ml). This concentrated solution was added dropwise to a large excess of Et_2O (700 ml). The resultant precipitate was collected by vacuum filtration and dried in vacuo to afford **11** as a bright-yellow powder (2.29 g, 77%). *Anal.* Calc. for $C_{27}H_{26}O_2P_2F_6Fe{\cdot}1/2H_2O$: C, 52.03; H, 4.36. Found: C, 51.77; H, 4.23%. ^{1}H NMR (CD_3NO_2): δ 7.73–7.55 (m, Ar*H*), 6.63 (d, *J*=7.2 Hz, H-3), 5.08 (br m, H-4), 2.48 (q, *J*=6.0 Hz, H-1), 2.44 (s, Me-2), 2.32 (dt, *J*=10.3, 4.8 Hz, H-5$_{exo}$), 1.88 (m, H-5$_{endo}$), 1.83 (d, *J*=6.1, Me-1). Peak assignments are made on the basis of 2D COSY-NMR spectra.

3.6. Dicarbonyl(3-methyl-2*E*,4*Z*-hexadiene)triphenylphosphineiron (12)

To a solution/suspension of cation **11** (200 mg, 0.325 mmol) in THF (15 ml) at 0°C was added solid $NaBH_3CN$ (22 mg, 0.35 mmol) in one portion. The mixture was stirred at 0°C for 1 h, warmed to r.t. and stirred at 23°C for 1 h. Water (15 ml) was added and the mixture was extracted with Et_2O (3×20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, 10:1 hexanes–ethyl acetate) to afford **12** as a yellow solid (80 mg, 52%). ^{1}H NMR ($CDCl_3$): δ 7.60–7.32 (m, Ar*H*), 3.68 (d, *J*=6.6 Hz, H-4), 2.02 (s, Me-3), 1.97–1.94 (m, H-2), 1.62–1.50 (m, H-5), 1.45 (dd, *J*=1.8, 6.5 Hz, Me-1), 1.06 (dd, *J*=1.8, 7.2, Me-6). ^{13}C{^{1}H} ($CDCl_3$): δ 136.5 (d, $J_{P□}$=37.6 Hz, Ar*C*), 133.1 (d, $J_{P□}$=9.7 Hz, Ar*C*), 129.3 (Ar*C*), 128.0 (d, $J_{P□}$=8.5, Ar*C*), 105.1 (C-3), 89.2 (C-4), 50.1 (d, $J_{P□}$=6.1 Hz) and 48.5 (d, $J_{P□}$=7.3 Hz, C-2 and C-5), 18.1 (Me-3), 16.4 (Me-1), 14.2 (Me-6).

3.7. Dicarbonyl [dimethyl (4′-methyl-2′*Z*,4′*E*-hexadienyl)propandioate]triphenylphosphineiron (13)

To a solution of lithium dimethyl malonate (0.68 mmol, freshly prepared from dimethylmalonate and n-butyl lithium) in THF (10 ml) at 0°C was added solid cation **11** (300 mg, 0.489 mmol) in one portion. The mixture was stirred at 0°C for 1 h and at 23°C for 18 h. Water (10 ml) was added and the mixture was extracted with Et_2O (3×20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, 3:1 hexanes–ethyl acetate) to afford **13** as a yellow oil (250 mg, 87%). ^{1}H NMR ($CDCl_3$): δ 7.52–7.33 (m, Ar*H*), 3.66–3.57, 3.60 and 3.55 (m and 2×s, H-3′ and 2×OMe), 2.96 (t, *J*=7.5 Hz, H-1), 2.29 (m, H-1′), 2.00 (s, Me-4′), 1.93 (m, H-5′), 1.69 (m, H-1′ and H-2′), 1.44 (dd, *J*=1.8, 6.3 Hz, Me-6′). ^{13}C{^{1}H} ($CDCl_3$): δ 214.0 and 213.7 (M□CO), 169.0 (*C*O$_2$Me), 135.8 (d, $J_{P□}$=37.8 Hz, Ar*C*), 132.8 (d, $J_{P□}$=9.7 Hz, Ar*C*), 129.3 (Ar*C*), 127.9 (d, $J_{P□}$=9.7 Hz, Ar*C*), 105.9 (C-4′), 86.7 (C-3′), 55.0 (*C*HE$_2$), 52.0 (OMe), 50.2 (d, $J_{P□}$=8.5 Hz) and 49.9 (d, $J_{P□}$=6.0 Hz, C-2′ and C-5′), 29.3 (C-1′), 17.9 (Me-4′), 16.2 (Me-6′).

3.8. Dicarbonyl (ethyl 6-methyl-2-nitro-4*Z*,6*E*-octadienoate)triphenylphosphineiron (14)

To a solution of lithium ethyl nitroacetate (0.34 mmol, freshly prepared from ethyl nitroacetate and n-butyl lithium) in THF (10 ml) at 0°C was added solid cation **11** (150 mg, 0.245 mmol) in one portion. The mixture was stirred at 0°C for 1 h and at 23°C for 18 h. Water (10 ml) was added and the mixture was extracted with Et_2O (3×20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, 3:1 hexanes–ethyl acetate) to afford **14** as a yellow oil (140 mg, 95%). This was determined to be an equimolar mixture of diastereomers by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$): δ 7.54–7.34 (m, Ar*H*), 4.69 and 4.59 (2×dd, *J*=5.1, 9.6 Hz, C*H*(NO_2)CO_2Et), 4.23–4.09 (m, O*C*$H_2$$CH_3$), 3.78 and 3.71 (2×d, *J*=7.2 Hz, H-5), 2.61 and 2.40 (2×m, H-3), 2.03 and 2.02 (2×s, Me-6), 1.85 (m, H-7), 1.62–1.38 (m, H-3′, H-4, Me-8′), 1.24 and 1.21 (2×t, *J*=7 Hz, CH_2C*H*$_3$). ^{13}C{^{1}H} ($CDCl_3$, diastereomeric signals in square brackets): δ 214.8 and 214.6 (M□CO), 164.9 [164.8] (C1), 136.4 [136.3] (d, $J_{P□}$=38.7 Hz, Ar*C*), 133.7 (d, $J_{P□}$=9.7 Hz, Ar*C*), 130.4 (Ar*C*), 129.0 (d, $J_{P□}$=9.6 Hz, Ar*C*), 107.3 [107.0] (C-6), 91.7 [91.0] (C-2), 86.7 (C-5), 63.5 (O*C*$H_2$$CH_3$), 50.9 and 47.9 (C-4 and C-7), 31.7 [31.5] (C-3), 18.8 (Me-6), 17.2 (Me-8), 14.6 (OCH_2*C*H_3).

3.9. Dicarbonyl (3-methyl-7-nitro-2E,4Z-heptadiene)triphenylphosphineiron (15)

To a solution of lithium nitromethane (1.22 mmol, freshly prepared from nitromethane and n-butyl lithium) in THF (10 ml) at 0°C was added solid cation **11** (500 mg, 0.814 mmol) in one portion. The mixture was stirred at 0°C for 1 h and at 23°C for 18 h. The reaction mixture was diluted with water and extracted with Et_2O (3×20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, 3:1 hexanes–ethyl acetate) to afford **15** as a yellow oil (256 mg, 59%). FAB-HRMS. Found: 473.1210. Calc. for $C_{26}H_{28}NO_2PFe$ (M-2CO): 473.1207. ^{1}H NMR ($CDCl_3$): δ 7.58–7.30 (m, Ar*H*), 4.09 (td, *J*=7.1, 12.3 Hz, H-7), 4.00 (td, *J*=7.1, 12.3, H-7′), 3.82 (br d, *J*=7.0 Hz, H-4), 2.26 (m, H-6), 2.06 (s, Me-3), 1.92–1.72 (m, H-2 and H-5), 1.49 (dd, *J*=2.0, 6.2, Me-1), 1.20 (m, H-6′). ^{13}C{^{1}H} ($CDCl_3$): δ 214.8 and 214.5 (M□CO), 136.6 (d, $J_{P□}$=38.9 Hz, Ar*C*), 133.8 (d, $J_{P□}$=9.2 Hz, Ar*C*), 130.5 (Ar*C*), 130.0 (d, $J_{P□}$=7.9 Hz, Ar*C*), 106.9 (C-3), 87.0 (C-4), 78.5 (*C*$H_2$$NO_2$), 50.1 (d, $J_{P□}$=7.8 Hz) and 49.2 (d, $J_{P□}$=8.2 Hz) (C-2 and C-5), 28.7 (C-6), 18.9 (Me-3), 17.2 (Me-1).

3.10. Preparation of 16 via nitrile oxide–allylbenzene cyclocondensation

To a solution of iron complex **15** (115 mg, 0.218 mmol), allylbenzene (31 mg, 0.26 mmol) and phenyl isocyanate (35 µl, 0.33 mmol) in benzene (10 ml) was added triethylamine (15 µl). The reaction mixture was stirred for 48 h, diluted with water (10 ml) and extracted several times with ether. The combined organic extracts were washed with H_2O, followed by brine, dried ($MgSO_4$) and concentrated. The product was extracted from the residue by dissolving in hexanes (in which the white crystalline by-product is not soluble). The combined hexane extracts were purified by column chromatography (SiO_2, 9:1 hexane–ethyl acetate to give **16** as a yellow oil (39.5 mg, 29%). This was determined to be an equimolar mixture of diastereomers by ^{1}H NMR spectroscopy. FAB-HRMS. Found: 573.1884. Calc. for $C_{35}H_{36}NOPFe$ (M-2CO): 573.1884. ^{1}H NMR ($CDCl_3$): δ 7.58–7.2 (m, Ar*H*), 4.61 (m, H-9), 3.78 and 3.75 (2×d, *J*=8.8 Hz, H-4), 2.94 and 2.92 (2×dd, *J*=5.8, 13.5 Hz, H-10), 2.7–2.2 (m, H-6, 2×H-8, 2×H-10), 2.04 and 2.03 (2×s, Me-3), 1.85 (m, H-2), 1.60 (br m, H6′), 1.45 (br d, *J*=5.5 Hz, Me-1).

3.11. Isoxazoline (17)

To a solution of iron complex **16** (11 mg, 0.017 mmol) in methanol (5 ml) was added ammonium cerium nitrate (10 mg, 0.018 mmol) and the mixture was stirred for 2 h at 23°C. The mixture was poured into water and this was extracted several times with ether. The combined ether extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, 10:1 hexanes–ethyl acetate) to afford **17** as a colorless oil (4 mg, 94%). ^{1}H NMR ($CDCl_3$): δ 7.35–7.15 (Ar*H*), 5.97 (d, *J*=11.3 Hz, H-4), 5.43 (br q, *J*=6.8 Hz, H-2), 5.26 (td, 7.6, 11.7, H-5), 4.81 (m, H-9), 3.25 (d, *J*=7.4 Hz, H-6, H-6′), 3.05 (dd, *J*=5.8, 13.8 Hz, H-10), 2.91 (dd, *J*=10.0, 17.1 Hz, H-8), 2.81 (dd, *J*=7.0, 13.8 Hz, H-10′), 2.64 (dd, *J*=7.4, 17.1 Hz, H-8′), 1.74 (s, Me-3), 1.68 (d, *J*=6.8 Hz, Me-1).

3.12. Preparation of 19 via nitrile oxide–triene cyclocondensation

To a solution of nitrodiene–iron complex **15** (388 mg, 0.733 mmol), triene–iron complex **18** (189 mg, 0.795 mmol) and phenyl isocyanate (120 µl, 1.1 mmol) in benzene (7 ml) was added triethylamine (50 µl). The reaction mixture was stirred for 36 h and then diluted with water (5 ml) and extracted several times with ether. The combined organic extracts were washed with H_2O, followed by brine, dried ($MgSO_4$) and concentrated. The product was extracted from the residue by dissolving in hexanes (in which the white crystalline by-product is not soluble). The combined hexane extracts were purified by column chromatography (SiO_2, 9:1 hexane–ethyl acetate) to give **19** as a golden-yellow foam (119 mg, 56%). *Anal.* Calc. for $C_{38}H_{36}NO_6PFe_2 \cdot 1/5C_6H_{14}$: C, 61.74; H, 5.13. Found: C, 62.08; H, 5.18%. M.p. 52–53°C. ^{1}H NMR ($CDCl_3$): δ 7.6–7.3 (m, Ar*H*), 5.17 and 5.16 (2×dd, *J*=4.5, 8.2 Hz, H-11), 5.08 and 5.06 (2×dd, *J*=4.5, 8.6 Hz, H-12), 4.09 and 4.07 (2×q, *J*=9.4 Hz, H-9), 3.86 and 3.83 (2×d, *J*=7.8 Hz, H-4), 2.8–2.2 (m, H-6, H-6′, H-8, H-8′), 2.06 (s, Me-3), 1.88 (m, H-2), 1.65 (m, H-5), 1.49–1.40 (m, Me-1, Me-14), 1.35 (m, H-10, H-13), additional signals due to entrained hexanes were observed. ^{13}C{^{1}H} ($CDCl_3$, diastereomeric signals in square brackets): δ 214.7, 214.4, 212.3 (M-CO), 160.7 (C-7), 136.6 (J_{CP}=38 Hz, Ar*C*), 133.7 (J_{CP}=9 Hz, Ar*C*), 130.3 (Ar*C*), 128.8 (J_{CP}=9 Hz, Ar*C*), 106.8 (C-3), 88.0 and 87.1 [87.0] (C4 and C-12), 83.9 [83.8] and 83.6 [83.5] (C9 and C11), 60.3 [60.1] and 59.8 [59.7] (C10 and C-13), 51.4 [51.3] and 49.8 (J_{CP}=9 Hz) [49.6 (J_{CP}=8 Hz)] (C-2 and C-5), 44.3 (C-8), 28.1 (C-6), 19.8, 18.7, 17.0 (Me-1, Me-3, Me-14).

3.13. Isoxazoline (22)

To a solution of bis-iron complex **19** (69.2 mg, 0.0939 mmol) in methanol (10 ml) was added ammonium cerium nitrate (102 mg, 0.19 mmol) and the mixture was stirred for 2 h at 23°C. The mixture was poured into water and extracted several times with ether. The combined ether extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, 10:1 hexanes–ethyl acetate) to afford **22** as a colorless oil (20.8 mg, 49%). ^{1}H NMR ($CDCl_3$): δ 6.24 (dd, *J*=10.4, 15.0 Hz, H-10), 6.00 (m, H-11), 5.99 (d, *J*=11.0 Hz, H-3), 5.76 (dq, *J*=14.8, 6.8 Hz, H-12), 5.57 (dd, *J*=7.6, 14.9 Hz, H-9), 5.45 (br q, *J*=6.7 Hz, H-1), 5.35 (td, 7.4, 11.2 Hz, H-4), 4.98 (br q, *J*=9.0 Hz, H8), 3.29 (d, *J*=7.1 Hz, H5, H5′), 3.05 (dd, *J*=10.4, 16.9 Hz, H7), 2.69 (dd, *J*=8.9, 16.8 Hz, H7′), 1.76 (d and s, Me-1 and Me-2), 1.68 (d, *J*=6.7 Hz, Me-12) [assignments based on COSY]. ^{13}C{^{1}H} ($CDCl_3$): δ 158.6, 136.8, 134.0, 133.2, 132.0, 131.0, 128.6, 126.3, 122.0, 81.6, 43.5, 28.1, 18.7, 17.0, 14.2.

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References

[1] (a) K. Gustafson, M. Roman, W. Fenical, J. Am. Chem. Soc. 111 (1989) 7519–7524. (b) S.D. Rychnovsky, D.J. Skalitzky, C. Pathirana, P.R. Jensen, W. Fenical, J. Am. Chem. Soc. 114 (1992) 671–677.

[2] (a) A.B. Smith III, G.R. Ott, J. Am. Chem. Soc. 120 (1998) 3935–3948. (b) Y. Kim, R.A. Singer, E.M. Carreira, Angew. Chem., Int. Ed. Engl. 37 (1998) 1261–1263. (c) R.J. Boyce, G. Pattenden, Tetrahedron Lett. 37 (1996) 3501–3504. (d) S.D. Rychnovsky, D.A. Pickering, Proceedings of the 207th National Meeting of the American Chemical Society, San Diego, American Chemical Society, Washington, DC, 1994, ORGN 209.

[3] V. Prahlad, W.A. Donaldson. Tetrahedron Lett., 37 (1996), pp. 9169-9172

[4] (a) B. Dasgupta, W.A. Donaldson, Tetrahedron: Asymmetry, 9 (1998) 3781–3788. (b) P.T. Bell, B. Dasgupta, W.A. Donaldson, J. Organomet. Chem. 538 (1997) 75–82.

[5] T. Le Gall, J.P. Lellouche, L. Toupet, J.-P. Beaucourt. Tetrahedron Lett., 47 (1989), pp. 6517-6520

[6] (a) W.A. Donaldson, L. Shang, C. Tao, Y.K. Yun, M. Ramaswamy, V.G. Young Jr., J. Organomet. Chem. 539 (1997) 87–98. (b) W.A Donaldson, M.-J. Jin, P.T. Bell, Organometallics 12 (1993) 1174–1179. (c) W.A. Donaldson, M.-J. Jin, Tetrahedron 49 (1993) 8787–8794. (d) W.A. Donaldson, J. Organomet. Chem. 395 (1993) 187–193.
[7] J.A.S. Howell, A.D. Squibb, A.G. Bell, P. McArdle, D. Cunningham, Z. Goldschmidt, H.E. Gottlieb, D. Hezroni-Langerman, R. Grée, Organometallics 13 (1994) 4336–4351.
[8] D. Seebach, F. Lehr, Angew. Chem., Int. Ed. Engl. 15 (1976) 505–506.
[9] (a) B.F.G. Johnson, J. Lewis, D.G. Parker, G.R. Stephenson, J. Organomet. Chem. 204 (1981) 221. (b) A.J. Pearson, M. Chandler, J. Organomet. Chem. 202 (1980) 175.
[10] T. Mukaiyama, T. Hoshino J. Am. Chem. Soc., 82 (1960), p. 5339
[11] (a) A.P. Kozikowski, A.K. Ghosh, J. Org. Chem. 49 (1984) 2762–2772. (b) A.P. Kozikowski, Y. Kitagawa, J.P. Springer, J. Chem. Soc., Chem. Commun. (1983) 1460–1462.