Journal of Organometallic Chemistry, 371 (1989) 219–231
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands
JOM 09979

New synthesis and reactions of a functionalized (η^4-butadienyl)tricarbonyliron complexed phosphonate

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(Received January 27th, 1989)

Abstract

The reaction of the isolated (η^5-pentadienyl)tricarbonyliron cation **2** with trimethylphosphite gives not only the (η^4-butadienyl)tricarbonyliron phosphonates **1** and **6** but also the σ–π allyl derivative **7**; the unusual regioselectivity of this nucleophilic addition is attributed to the presence of the ester group in **2**. A new and efficient synthesis of **1** has been devised based upon the in situ trapping of a transient (η^5-pentadienyl) complexed cation by $P(OMe)_3$. The reactions of **1** with two aldehydes have been studied. Low temperature bond-shift isomerizations of the initially-produced trienes complexed by $Fe(CO)_3$ are observed in several cases.

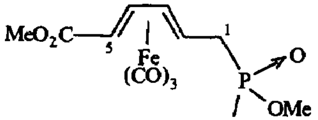
Introduction

Unsymmetrical trienes or polyenes selectively complexed by $Fe(CO)_3$ are very useful intermediates in organic synthesis [1]. Starting from such complexes many compounds, including natural products, have been prepared, often in a chiral form, by taking advantage of the strong protecting and stereodirecting properties of the $Fe(CO)_3$ moiety [2,3].

Three methods have been described for the preparation of such organometallic derivatives. Direct complexation of polyenes suffers from low yields and usually lacks regioselectivity [1]. The Wittig type reaction between complexed aldehydes and phosphoranes is the method of choice in most cases [1]. The "reverse" approach, i.e.

reaction of complexed phosphoranes or phosphonate carbanions with carbonyl derivatives, has been much less studied [4,5]. Such phosphonates are of special interest when complexed trienes with a free double bond of *E* configuration are needed; these complexes react with aliphatic and aromatic aldehydes to give exclusively *trans* olefins [4,5].

As part of our program directed towards the synthesis and biological evaluation of leukotrienes selectively complexed by $Fe(CO)_3$ [6*] we needed the (η^4-butadienyl)tricarbonyliron phosphonate (**1**), bearing an ester group in position 5.



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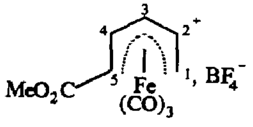

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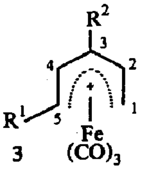
We describe here: (i) the unusual reaction of the cation **2** with $P(OMe)_3$, which reveals the strong effect of the ester group on the regioselectivity of the nucleophilic addition; (ii) a new and efficient synthesis of **1**; and (iii) the results of a study of the reactions of the carbanion derived from **1** with two selected aldehydes.

Results and discussion

The only species containing phosphonates linked to a butadiene tricarbonyliron complex described previously were **4a**, **5** [4], **5b** [5] and **4c** [7]. They were prepared



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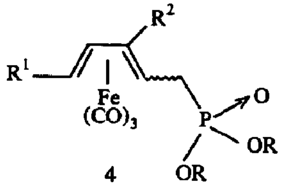

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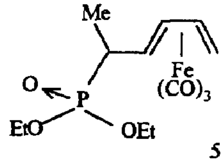

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(**a**: $R^1 = Me$; $R^2 = H$; $R = Et$; **b**: $R^1 = n-C_4H_9$; $R^2 = H$; $R = Me$; **c**: $R^1 = CO_2Et$; $R^2 = Me$; $R = Et$)

by reaction of the η^5-complexed pentadienyl cations **3** with $P(OR)_3$; the *anti* derivative, which is first obtained, can be smoothly transformed under basic conditions into the *syn* isomer [4,5]. In the case of **3a**, a (5/4) mixture of **4a** (attack on C1) and **5** (addition at C5) was obtained [4]. The reaction was regiospecific in the case of **3b** (exclusive addition at C1 yielding **4b**) [5]. The same reaction applied to the easily accessible cation **2** [8] gives a mixture of **1**, **6** and **7** in a (5/1/4) ratio (40% overall yield).

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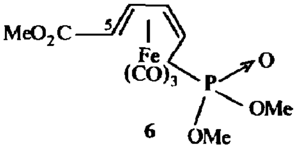
* Reference number with asterisk indicates a note in the list of references.

Table 1

Bond distances (Å)

Fe–C1	2.109(1)	O6–C9	1.370(4)
Fe–C2	2.065(1)	O7–C6	1.197(2)
Fe–C3	2.146(1)	O8–C6	1.321(2)
Fe–C4	2.682(1)	O8–C7	1.436(2)
Fe–C5	2.132(1)	C1–C2	1.373(3)
Fe–C10	1.758(2)	C1–H1A	0.89(2)
Fe–C11	1.788(2)	C1–H1B	0.92(2)
Fe–C12	1.840(2)	C2–C3	1.384(2)
P–O4	1.467(1)	C2–H2	0.91(2)
P–O5	1.569(1)	C3–C4	1.512(2)
P–O6	1.534(1)	C3–H3	0.88(2)
P–C4	1.802(1)	C4–C5	1.493(2)
O1–C10	1.124(2)	C5–H5	0.992(15)
O2–C11	1.139(2)	C4–H4	0.80(2)
O3–C12	1.138(2)	C5–C6	1.481(2)
O5–C8	1.403(2)		



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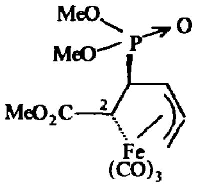

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A mixture of the *syn*-**1** and the *anti* phosphonate **6** was separated from **7** by chromatography and characterized by NMR spectroscopy. The structure of **6** was further confirmed by the smooth isomerization of this (**1** + **6**) mixture into **1** under basic conditions (MeONa, MeOH).

The σ–π allyl structure of **7** was unambiguously established by a single-crystal X-ray diffraction study (see Tables 1, 2 and 3) and an ORTEP drawing of its structure is shown in Fig. 1. Particularly relevant is the fact that the four bond distances Fe–C1, Fe–C2, Fe–C3 and Fe–C5 are very close (2.06 to 2.13 Å) and shorter than Fe–C4 (2.68 Å). The C1–C2–C3 bond angle (124.9°) is also in excellent agreement with a π-allyl type system and quite different from the C3–C4–C5 bond angle (105.2°).

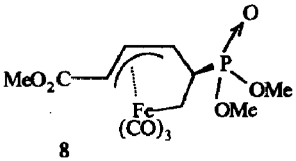
The reaction of $P(OMe)_3$ with cation **2**, to give **7** thus occurred at carbon 4 and *anti* to the $Fe(CO)_3$ unit. Nucleophilic additions at internal carbon atoms of η^5-pentadienyl complexed cations have been reported for several cyclic complexes [9,10], but it is unusual in the case of acyclic derivatives, and to the best of our knowledge there are only three other examples, namely: hydride addition to an η^5-pentadienyltricarbonyliron cation [11], a carbanion addition to a cation whose iron had three phosphines as ligands [12], and attack of a malonate carbanion on cation **2** [13*]. Thus, the present reaction is the first example of C4 addition in the case of a phosphorus nucleophile. This unusual reactivity clearly indicates that the regioselectivity of the nucleophilic additions on η^5-complexed pentadienyl cations depends on at least [14*] two factors:

Table 2

Bond angles (°)

C2–Fe–C10	128.03(8)	C1–C2–C3	124.1(1)
C2–Fe–C11	128.22(8)	C1–C2–C3	117.0(1)
C2–Fe–C12	86.24(7)	C3–C2–H2	117(1)
C10–Fe–C11	102.92(8)	C2–C3–C4	124.9(1)
C10–Fe–C12	94.24(8)	C2–C3–H3	120(1)
C11–Fe–C12	92.10(9)	C4–C3–H3	114(1)
O4–P–O5	115.96(8)	P–C4–C3	116.9(1)
O4–P–O6	115.03(7)	P–C4–C5	116.0(1)
O4–P–C4	114.83(7)	P–C4–H4	102(1)
O5–P–O6	99.99(8)	C3–C4–C5	105.2(1)
O5–P–C4	103.32(7)	C3–C4–H4	110(1)
O6–P–C4	105.94(7)	C5–C4–H4	107(1)
P–O5–C8	123.9(1)	C4–C5–C6	113.8(1)
P–O6–C9	123.1(2)	C4–C5–H5	115.6(9)
C6–O8–C7	115. (2)	C6–C5–H5	109.9(9)
H1A–C1–H1B	111. (1)	O8–C6–C5	110.2(1)
C2–C1–H1A	123. (1)	O7–C6–O8	122.8(1)
C2–C1–H1B	120. (1)	O7–C6–C5	127.0(2)
Fe–C2–C1	72.53(9)	Fe–C10–O1	177.2(2)
Fe–C2–C3	74.01(9)	Fe–C11–O2	177.5(2)
Fe–C2–H2	114. (1)	Fe–C12–O3	178.2(2)

(i) The electronic structure of the complexed cation: it has been shown recently by Bleeke and Hays that the nature of the ligands on the iron plays a role [12]. This is also true for the substituents on the cation itself; whereas alkyl-substituted cations give either C1 or C5 attack (or both) [15*] the ester group in **2** directs 40% of the trimethylphosphite reaction towards C4. Noteworthy also is the fact that no reaction on C2 was observed; such a reaction would give **8**, an isomer of **7**.



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(ii) The nature of the nucleophile: whereas H_2O (a hard nucleophile) reacts exclusively with **2** via C4 addition [8], trimethylphosphite (which is a soft nucleophile) gave 40% of C4 addition [16*]. Of special interest is the fact that this is the opposite trend to that observed during the nucleophilic addition to dicarbonyl(triphenylphosphine) and dicarbonyl(triphenylphosphite)cycloheptadienyliron salts [10].

These results indicate that a full understanding of the factors governing the regioselectivity of the nucleophilic additions on η^5-pentadienyl complexed cations not only requires the study of various nucleophiles but also of differently substituted cations; simple derivatives such as **2** or **3** thus appear to be useful models.

Our failure to prepare the complexed phosphonate **1** in a good yield led us to investigate the attractive methodology recently developed by Uemura and his coworkers [17]. This, regiospecific, Lewis-acid-catalyzed carbon–carbon bond formation uses the in situ trapping of a transient transoid (η^5-pentadienyl)tri-

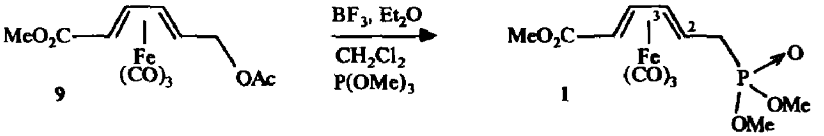
Table 3

Atomic coordinates, with estimated standard deviations

Atom	*x*	*y*	*z*	*B* (Å^2) ^{a}
Fe	0.79901(2)	0.8261(5)	0.39753(2)	3.652(8)
P	0.58487(4)	0.2926(1)	0.14283(4)	3.61(1)
O1	0.9889(2)	0.2305(4)	0.4537(2)	7.29(7)
O2	0.8244(2)	−0.2774(3)	0.3465(2)	7.65(8)
O3	0.8289(2)	−0.0253(5)	0.5943(2)	8.70(8)
O4	0.5929(1)	0.3049(4)	0.0505(1)	5.69(5)
O5	0.6077(2)	0.4643(3)	0.2040(2)	6.16(6)
O6	0.4833(1)	0.2536(4)	0.1376(2)	5.67(5)
O7	0.7802(2)	−0.0601(3)	0.1506(2)	6.52(6)
O8	0.9026(1)	0.1184(3)	0.2226(2)	5.68(5)
C1	0.7453(2)	0.3310(4)	0.4416(2)	4.83(7)
C2	0.6751(2)	0.2054(4)	0.3916(2)	4.61(6)
C3	0.6472(2)	0.0958(4)	0.3133(2)	4.08(6)
C4	0.6627(2)	0.1326(4)	0.2232(2)	3.38(5)
C5	0.7683(2)	0.1646(3)	0.2552(2)	3.24(5)
C6	0.8142(2)	0.0613(4)	0.2026(2)	4.25(6)
C7	0.9559(2)	0.0213(7)	0.1792(3)	8.0(1)
C8	0.5939(3)	0.6333(5)	0.1651(3)	6.6(1)
C9	0.4211(4)	0.1411(8)	0.0725(4)	11.5(1)
C10	0.9158(2)	0.1689(5)	0.4326(2)	4.80(7)
C11	0.8128(2)	−0.1370(4)	0.3645(2)	4.91(7)
C12	0.8159(2)	0.0154(5)	0.5187(2)	5.66(8)
H1A	0.753(2)	0.395(3)	0.366(2)	4 *
H1B	0.766(2)	0.390(4)	0.469(2)	4 *
H2	0.657(2)	0.175(4)	0.440(2)	4 *
H3	0.606(2)	0.011(4)	0.307(2)	4 *
H4	0.651(2)	0.047(3)	0.191(2)	4 *
H5	0.788(2)	0.289(3)	0.258(2)	4 *
H7A	1.009(2)	0.050(3)	0.205(2)	4 *
H7B	0.930(2)	0.026(4)	0.119(2)	4 *
H7C	0.968(2)	−0.089(4)	0.213(2)	4 *
H8A	0.541(2)	0.631(4)	0.101(2)	4 *
H8B	0.645(2)	0.648(4)	0.147(2)	4 *
H8C	0.605(2)	0.720(3)	0.221(2)	4 *
H9A	0.398(2)	0.242(4)	0.041(2)	4 *
H9B	0.435(2)	0.112(4)	0.027(2)	4 *
H9C	0.417(2)	0.088(3)	0.096(2)	4 *

^{a} Starred atoms were refined isotropically. Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as: $\frac{4}{2}(a^2B_{1,1} + b^2B_{2,2} + c^2B_{3,3} + ab(\cos\gamma)B_{1,2} + ac(\cos\beta)B_{1,3} + bc(\cos\alpha)B_{2,3}]$.

carbonyliron cation by various carbon nucleophiles. This reaction was satisfactorily extended to the phosphorus nucleophiles (eq. 1).



The acetate **9**, prepared (95% yield) from the corresponding alcohol [8], reacted with an excess of P(OMe)$_3$ in the presence of boron trifluoride etherate to give **1** in

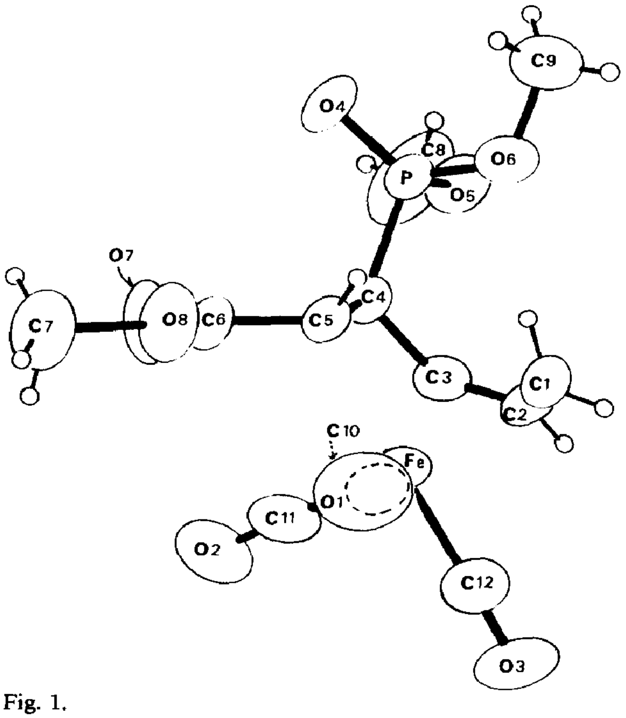
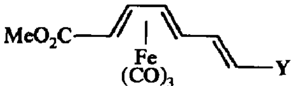


Fig. 1.

90% yield as the only isolated product [18*]. In agreement with the results observed with the carbon nucleophiles, the reaction was regiospecific (the phosphonate is located on the carbon previously bearing the acetoxy group) and stereospecific: the J_{23} coupling constant (8.1 Hz) confirms the *syn* structure.

The reactions of **1** with two representative aldehydes were then examined, namely glyoxalmonodiethyl acetal [19] and formaldehyde. The trienes **10**, bearing two different functions, ar very useful intermediates for the synthesis of selectively-complexed polyenes [20*].



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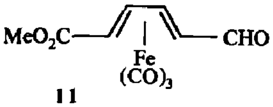


11

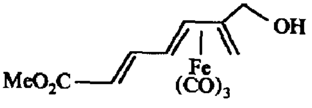
a : Y = CH(OEt)$_2$; **b** : Y = CHO

The reaction of **11** with formylmethylenetriphenylphosphorane gave **10b**, but only in low yields (20–30%) and after tedious chromatographic separations [21]. In contrast, reaction of **1** with glyoxalmonodiethylacetal, under the previously described reaction conditions (NaH, DME) [5] gave only **10a**, which after removal of the acetal group [22] yielded **10b** (61% overall from **1**). The *E* isomer was the only isolated derivative and there was no bond-shift during this reaction.

The complexed triene **12** also represents an attractive model for studies of the diastereoselectivity of several reactions, including cycloadditions. It was obtained, but only in very low yield (< 10%), by reaction of **11** with methylenetriphenylphosphorane [23]. Thus we examined the reaction of the carbanion derived from **1** with paraformaldehyde; the results strongly depended upon the reaction conditions and especially on the base used. Use of the same conditions as before (NaH, DME) gave a mixture of **12** (25%), **13** (27%) and **14** (44% yield), separated by chromatography and characterized spectroscopically.


12


13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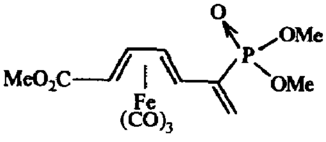
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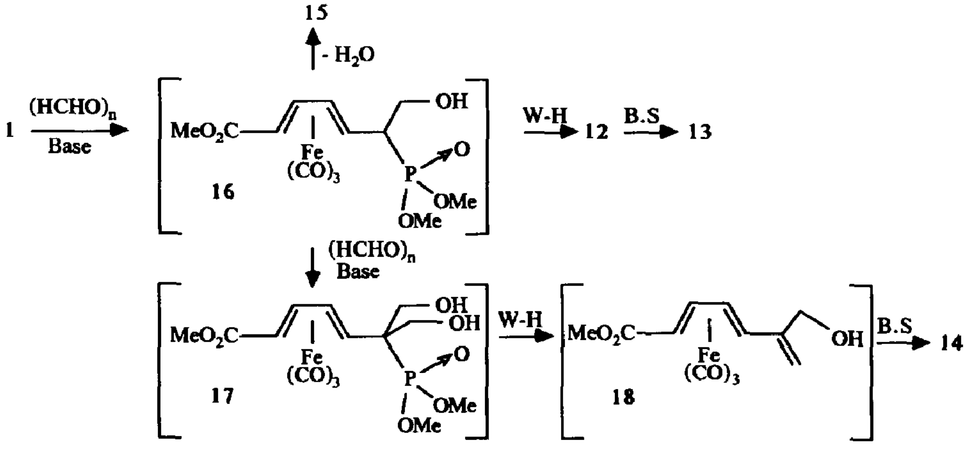
Particularly relevant in the case of the bond-shifted derivatives are the vinylic protons at 5.88 (d, *J* 15.2 Hz) for **13** and 5.90 (d, *J* 15.6 Hz) for **14**. Control experiments established that **12** slowly isomerized into **13** under the reaction conditions. Although thermal bond-shift isomerizations of acyclic polyenes complexed by $Fe(CO)_3$ have been studied in detail [1,20*], such low temperature isomerizations have been reported only twice: in one case it occurred when strongly basic nucleophiles were used [24,25], and in the other $BF_3 \cdot OEt_2$ was the catalyst [26]. Thus our preparation represents the first time that sodium hydride has been shown to induce such a reaction.

Use of phase transfer catalytic conditions gave a different result, since the desired compound **12** (26% yield) was obtained, together with the vinyl phosphonate **15** (11%) and recovered starting material **1** (30%). They were separated by flash-chromatography and the structure of **15** was established by NMR spectroscopy: noteworthy are the two vinylic protons, with their ^3J(PH) coupling constants of 48.2 Hz (*trans*) and 23.3 Hz (*cis*) [27]. Interestingly, there was no bond shift in the case of **12** under the PT conditions, since no **13** was detected in the reaction mixture.

The mechanism we propose for the formation of these compounds is given in Scheme 1. The first adduct **16** gives **12** via the normal Wittig–Horner type reaction;



Scheme 1. W-H = Wittig–Horner reaction; B.S.: bond-shift isomerization.

depending upon the reaction conditions this latter derivative may or may not give the bond-shifted isomer **13**. The intermediate **16** can also lose water to give **15**. As observed for other phosphonate carbanions [28], **16** can react with a second molecule of formaldehyde to give the bis-adduct **17**; a Wittig–Horner reaction followed by a bond-shift leads to the isolated product **14**.

Concluding remarks

Very few studies have dealt with the reactions of acyclic (η^5-pentadienyl)tricarbonyliron cations bearing electron-withdrawing substituents. The unusual reactivity of **2** towards $P(OMe)_3$, which yields in part the σ–π allyl derivative **7**, appears to be due to the presence of the ester group. Thus, further studies (including theoretical calculations) are necessary for a better understanding of the factors which govern the nucleophilic additions to such cations. The method devised by Uemara was successfully extended to phosphorus nucleophiles, providing a quick and efficient synthesis of **1**. The low temperature bond-shift isomerizations observed during the preparation of trienes complex by $Fe(CO)_3$, starting from **1**, confirm that great care has to be taken during the synthesis of such species when strongly basic conditions have to be used.

Experimental section

General information

NMR spectra were recorded on a Jeol FX90 (^{1}H: 90 MHz; ^{13}C: 22.5 MHz) or a Bruker AM 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) spectrometer equipped with an Aspect 3000 computer system. Chemical shifts are shown in δ units, coupling constants in Hz. Infrared spectra were recorded on a Beckman 4250 or a Pye Unicam SP3-200 spectrophotometer. Liquid chromatography under medium pressure (10 bars) was carried out with a Jobin–Yvon liquid chromatograph packed with Merck silica gel H (25–45 mμ). Flash-chromatography was as described by Still, Kahn and Mitra [29]. Routine analytical thin layer chromatography was carried out on precoated 60 F_{254}-Merck thin layer plates. Anhydrous solvents and reagents were dried under standard procedures and kept under nitrogen in the presence of 3Å or 4Å molecular sieves.

Reaction of $P(OMe)_3$ with the methoxycarbonyl-5-(η^5-pentadienyl)tricarbonyliron cation 2

To a solution of the cation **2** [8] (1 g, 2.85 mmol) in anhydrous CH_2Cl_2 (20 ml) under nitrogen at 0 °C was added freshly distilled $P(OMe)_3$ (750 mg, 6.05 mmol). After 3 h stirring at this temperature, the mixture was concentrated under vacuum and subjected to medium pressure liquid chromatography with a (1/4) mixture of hexane and ethyl acetate as eluent. A 1/1 mixture of the phosphonates **1** and **6** was collected (**1** + **6**: 256 mg; 24%), and then the σ–π allyl derivative **7** (170 mg; 16%) as yellow crystals (m.p. 64 °C).

The spectral data for **1** are presented later below. The main NMR data for **6**, obtained from the spectrum of the **1** + **6** mixture, were as follows: ^{1}H NMR (300 MHz, $CDCl_3$): 6.07 (dd, 1H, *J* 8.5, 5.0, H4); 5.40 (dd, 1H, *J* 7.1, 5.0, H3); 3.80 (s, 3H, CO_2Me); 3.74 (d, 3H, ^3J(PH) 5.0, P-O*Me*); 3.70 (d, 3H, ^3J(PH) 5.0, P-O*Me*);

2.85 (m, 1H, H2); 2.12 (ddd, 1H, *J* 3.4, 13.0, ^{2}J(PH) 21.0, H1); 2.05 (d, 1H, *J* 9.0, H5); 1.45 (ddd, 1H, *J* 13.0, 15.0, ^{2}J(PH) 21.0, H1).

The spectral data for **7** are as follows: ^{1}H NMR (300 MHz, $CDCl_3$): 4.65 (ddd, 1H, *J* 12.0, 12.0, 7.5, H5); 4.30 (dd, 1H, *J* 12.0, 7.3, H4); 3.80 (m, 2H, H3, H6 *syn*); 3.70 (s, 3H, CO_2*Me*); 3.65 (d, 3H, ^{3}J(PH) 14.5, P-O*Me*); 3.62 (d, 3H, ^{3}J(PH) 14.5, P-O*Me*); 3.10 (d, 1H, *J* 12.0, H6 *anti*); 0.55 (dd, 1H, *J* 11.5, ^{3}J(PH) 7.5, H2). ^{13}C NMR (75 MHz, $CDCl_3$): 210.16 (s, Fe-CO); 209.67 (s, Fe-*C*O); 203.03 (d, *J*(CP) 6.4, Fe-*C*O); 180.09 (s, *C*O_2Me); 99.73 (dd, ^{1}J 156.6, ^{3}J(CP) 4.6, C5); 56.49 (d, ^{1}J 156.0, C4); 55.64 (t, ^{1}J 156.0, C6); 52.93 (qd, ^{1}J 147.9, ^{2}J(CP) 5.2, P-O*Me*); 52.86 (qd, ^{1}J 147.9, ^{2}J(PC) 5.2 P-O*Me*); 51.73 (q, CO_2*Me*, ^{1}J 146.2); 36.14 (dd, ^{1}J 130,0, ^{1}J(CP) 130.8, C3); 3.35 (dd, ^{1}J 149.0, ^{2}J(CP) 6.5, C2). IR (mull, cm^{-1}): 2065 and 1990 (C≡O), 1700 (C=O).

X-ray diffraction study of 7. $FePC_{12}H_{15}O_8$, $Mr = 374.1$, $P2_1/c$, *a* 15.113(6), *b* 7.643(4), *c* 15.288(6) Å, β 113.23(3)°, *V* 1622(1) Å, $Z = 4$, $D_x = 1.53$ Mg m^{-3}, λ (Mo-K_α) 0.71069 Å, $\mu = 10.56$ cm^{-1}, F(000) = 768, $T = 296$ K. An Enraf-Nonius automatic diffractometer was used. The cell parameters are determined and refined with a set of 25 high-θ reflexions. The sample (prism 0.25 × 0.30 × 0.30 mm) gives 2239 independent reflexions ($R_{INT} = 0.017$) with $I > \sigma(I)$. The Fe atom was located from a Patterson Map. The remaining non-hydrogen atoms were found by successive scale-factor refinement and Fourier difference maps. After isotropic ($R = 0.10$) then anisotropic ($R = 0.048$) refinement, the hydrogen atoms were found between 0.62 and 0.24 eÅ^{-3}. Full-matrix least-square refinement gave $R = 0.039$, $R = 0.035$.

Bond distances are shown in Table 1, bond angles and distances in Table 2, and atomic coordinates in Table 3. Lists of thermal parameters and structure factors are available from the authors.

Synthesis of [2-methoxycarbonyl-(2,3,4,5-η^4)-2E,4E-pentadienyl]irontricarbonyl-6-acetoxy (9)

Pyridine (12 ml) was slowly added to the diene tricarbonyliron complexed alcohol [8] (505 mg, 1.79 mmol) in acetic anhydride (8 ml) at 0 °C. After 14 h stirring at room temperature, the mixture was concentrated under reduced pressure. The acetate **9** was purified by medium pressure liquid chromatography with a 9/1 mixture of low boiling petroleum ether/ether as eluent: **9** (551 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): 5.85 (dd, 1H, *J* 8.5, 5.0, H_3); 5.45 (dd, 1H, *J* 8.5, 5.0, H_4); 4.20 (dd, 1H, *J* 11.6, 8.3, H_6); 4.05 (dd, 1H, *J* 11.6, 6.6, H_6); 3.65 (s, 3H, CO_2*Me*); 2.05 (s, 3H, OCO*Me*); 1.30 (m. 1H, H_5); 1.10 (d, 1H, *J* 8.5, H_2). ^{13}C NMR (22.5 MHz, $CDCl_3$): 210.30 (s, Fe-*C*O); 172.19 (s, *C*O_2Me); 170.43 (s, O-*C*OMe); 86.47 (d, *J* 169.2, C4); 84.68 (d, *J* 174.6, C3); 65.40 (td, ^{1}J 148.0, ^{2}J 4.7, *C*H_2); 56.67 (d, *J* 161.8, C5); 51.67 (q., *J* 147.0, CO_2*Me*); 46.63 (dd, ^{1}J 164.5, ^{2}J 8.1, C2); 20.68 (q, *J* 129.6, OCO*Me*). IR (film, cm^{-1}): 2060 and 1990 (C≡O); 1770 and 1710 (C=O).

Synthesis of [tricarbonyl-5-methoxycarbonyl-(2,3,4,5-η^4)-2E,4E-pentadienyliron]-yl-1 phosphonic acid dimethyl ester (1)

An excess of freshly distilled trimethylphosphite (460 mg, 3.7 mmol) was added under nitrogen to a cold (0 °C) solution of the acetate **9** (389 mg, 1.2 mmol) in anhydrous CH_2Cl_2 (10 ml) was added under nitrogen. The mixture was cooled to −78 °C and a 50% ethereal solution of the complex $BF_3 \cdot OEt_2$ (450 μl, 4.88 mmol) was slowly added. After 7 h stirring at room temperature and concentration under reduced pressure, the phosphonate **1** was purified by medium pressure liquid chromatography with a 1/4 mixture of hexane and ethyl acetate as eluent: **1** was obtained as a yellow oil (404 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): 5.85 (dd, 1H, J 8.0, 5.0, H3); 5.30 (dd, 1H, J 8.0, 5.3, H4); 3.78 (d, 6H, ^3J(PH) 10.3, P-O*Me*); 3.68 (s, 3H, CO_2*Me*); 2.20 (ddd, 1H, J 15.0, 5.9; ^2J(PH) 20.2, H1); 2.05 (ddd, 1H, J 15.2, 8.6 ^2J(PH) 20.2, H1); 1.30 (m, 1H, H2); 1.05 (d, 1H, J 8.2, H5). ^{13}C NMR (22.5 MHz, $CDCl_3$): 209.70 (s, Fe-*C*O); 172.2 (s, *C*O_2Me); 87.57 (dd, ^1J 169.2, ^3J(CP) 9.4, C3); 84.26 (d, J 175.2, C4); 52.77 (qd, ^1J 148.0, ^2J(CP) 6.7, P-O*Me*); 52.59 (qd, ^1J 148.0, ^2J(CP) 6.7, P-O*Me*); 51.99 (q, J 146.4, CO_2*Me*); 51.64 (d, J 172.5, C2); 46.30 (dd, ^1J 164.5, ^2J 8.1, C5); 30.18 (dt, ^1J 128.2, ^1J(CP) 138.3, C1). IR (film, cm^{-1}): 2060 and 1980 (C≡O), 1710 (C=O).

*Reaction of **1** with glyoxalmonodiethylacetal*

To a cold (−30 °C) suspension of NaH (60% suspension in mineral oil, 11 mg, 0.27 mmol) in anhydrous dimethoxyethane (1 ml) a solution of **1** (49 mg, 0.13 mmol) in anhydrous DME was added dropwise under nitrogen. The deep red mixture was stirred for 1 h at 0 °C and then cooled to −30 °C. HMPA (0.3 ml) was then added, followed by a solution of glyoxalmonodiethyl acetal [19] (0.069 ml, about 0.52 mmol) in DME (1.2 ml). After 3 h stirring at room temperature, the mixture was quenched with saturated aqueous ammonium chloride and the organic material extracted twice with ether. The combined organic phases were washed three times with brine and dried ($MgSO_4$). After removal of the solvents under reduced pressure, the (NMR pure) acetal **10a** (38 mg) was characterized from its spectroscopic data and used directly for the next step. **10a**: ^{1}H NMR (90 MHz, $CDCl_3$): 5.92 to 5.71 (m, 3H, H3, H6, H7), 5.42 (dd, 1H, J 9.3, 5.0, H4); 4.84 (d, 1H, J 3.4, H8); 3.67 (s, 3H, CO_2*Me*); 3.55 (m, 4H, O*C*H_2CH_3); 2.04 (dd, 1H, J 9.3, 9.3, H5); 1.28to 1.12 (m, 7H, OCH_2C*H_3* and H2). IR (film, cm^{-1}): 2060 and 1990 (C≡O); 1720 (C=O).

The removal of the acetal group was performed by use of wet silica gel and 1% H_2SO_4, as previously described [22]. Starting from 202 mg of the preceding crude **10a**, 169 mg of **10b** were obtained after flash-chromatography on SiO_2 (overall yield from **1** 61%). **10b**: ^{1}H NMR (90 MHz, $CDCl_3$): 9.46 (d, 1H, J 7.5, *CHO*); 6.66 (dd, 1H, J 15.2, 9.2, H6); 6.22 (dd, 1H, J 15.2, 7.5, H7); 5.96 (dd, 1H, 8.1, 5.0, H3); 5.65 (dd, 1H, J 9.2, 5.0, H4); 3.70 (s, 3H, CO_2*Me*); 1.99 (dd, 1H, J 9.2, 9.2, H5); 1.49 (d, 1H, J 8.1, H2). IR (film, cm^{-1}): 2070 and 1995 (C≡O); 1710 and 1680 (C=O); 1615 (C=C).

*Reaction of **1** with paraformaldehyde using NaH as a base*

Sodium hydride (60% suspension in mineral oil, 22 mg, 0.55 mmol) was washed twice with petroleum ether under nitrogen. After addition of DME (2 ml) the mixture was cooled to −30 °C and a solution of the phosphonate **1** (100 mg, 0.264 mmol) in DME (5 ml) was added. The deep red mixture was stirred under nitrogen for 1 h at 0 °C then cooled again to −20 °C before the addition of paraformaldehyde (45 mg, 1.5 mmol) in a mixture of HMPA (1 ml) and DME (2 ml). The mixture was allowed to warm slowly (45 min) to room temperature and then stirred for a further 195 min.

After addition of saturated aqueous ammonium chloride (20 ml) the organic material was extracted three times with ether. The combined organic layers were washed three times with water and dried ($MgSO_4$). The solvents were removed under vacuum and three products were separated by flash chromatography with a 5/95 mixture of ether and petroleum ether as eluent.

12 (orange viscous oil; 18.5 mg, 25%). ^{1}H NMR (90 MHz, $CDCl_3$): 6.02 to 5.01 (m, 5H, H3, H4, H6, H7), 3.66 (s, 3H, CO_2Me); 2.07 (dd, 1H, J 9.2, 9.2, H5); 1.22 (d, 1H, J 8.1, H2). ^{13}C NMR (22.5 MHz, $CDCl_3$): 209.5 (s, Fe-*C*O); 172.49 (s, *C*O_2Me); 138.015 (d, J 157.1, C6); 116.3 (t, J 160.1, C7); 85.13 (d, J 168.5, C4); 83.43 (d, J 175.2, C3); 63.08 (d, J 160.0, C5); 51.63 (q, J 147.0, CO_2Me); 45.77 (dd, ^1J 164.5, ^2J 8.1, C2). IR (film, cm^{-1}): 2060 and 1990 (C≡O), 1720 (C=O), 1630 (C=C).

13 (orange crystals; m.p. 97 °C, 20 mg, 27%). ^{1}H NMR (90 MHz, $CDCl_3$): 6.84 (dd, 1H, J 15.2, 10.4, H3); 5.88 (d, 1H, J 15.2, H2); 5.63 to 5.20 (m, 2H, H5, H6); 3.71 (s, 3H, CO_2Me); 1.96 (ddd, 1H, J 7.0, 2.8, 1.0, H7 *syn*); 1.64 (dd, 1H, J 10.4, 8.6, H4), 0.73 (dd, 1H, J 9.4, 2.8, H7 *anti*). ^{13}C NMR (22.5 MHz, $CDCl_3$): 210.30 (s, Fe-*C*O); 166.86 (s, CO_2Me); 148.68 (d, J 152.4, C3); 118.40 (d, J 157.8, C2), 87.33 (d, J 170.0, C6); 83.40 (d, J 171.2, C5); 56.91 (d, J 159.1, C4); 51.40 (q, J 147.0, CO_2Me); 40.64 (tdd, ^1J 160.1, ^2J 7.4, ^3J 3.4, C7). IR (HCB, cm^{-1}): 2050 and 1980 (C≡O), 1710 (C=O), 1625 (C=C).

14 (yellow oil, 36 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$): 6.85 (dd, 1H, J 15.6, 11.3, H3); 5.90 (d, 1H, J 15.6, H2); 5.65 (d, 1H, J 7.7, H5); 4.55 (d, J 16.5) and 4.20 (d, J 16.5) (2H, CH_2OH); 3.75 (s, 3H, CO_2Me); 2.05 (d, 1H, J 1.0, H7 *syn*); 1.9 (s, O*H*); 1.60 (dd, 1H, J 10.5, 9.7, H4); 0.65 (d, 1H, 1.0, H7 *anti*). IR (film, cm^{-1}): 3300 (OH), 2060 and 1980 (C≡O), 1710 (C=O). CI mass spectrum: $[M+H+NH_3]^+$ m/z 326.0 (44%); $[M+H]^+$ 309.0 (13%); $[M+NH_4-CO]^+$ m/z 298.0 (6%).

NaH-induced isomerization of 12 into 13

To a suspension of NaH (60% in mineral oil, 19 mg, 0.475 mmol) in anhydrous DME under nitrogen at −25 °C was added a solution of **12** (86 mg, 0.31 mmol) in anhydrous DME (5 ml). After 8 h stirring at room temperature, the mixture was quenched with saturated aqueous ammonium chloride and the organic material extracted three times with ether. The combined organic layers were washed three times with water and dried ($MgSO_4$), and the solvents were removed under vacuum. Flash-chromatography with a (1/4) mixture of ether and petroleum ether as eluent yielded **13** (44 mg, 51%) and recovered starting material **12** (27 mg, 31%).

Reaction of 1 with paraformaldehyde under phase transfer catalytic conditions

To a solution of **1** (101 mg, 0.27 mmol) in CH_2Cl_2 (1 ml) was added formaldehyde (67 μl of a 37% commercially available aqueous solution) followed by triethylbenzylammonium chloride (16 mg, 0.07 mmol) and NaOH (36 μl of a 50% aqueous solution). The mixture was vigorously stirred, rapidly becoming deep red. After 75 min further formaldehyde (60 μl) was added, and the mixture was stirred for six further hours, than extracted twice with ether. The combined organic layers were washed three times with water, dried ($MgSO_4$), and concentrated in vacuo.

Flash-chromatography on SiO_2 with mixtures of ether and petroleum ether (1/4) and then dichloromethane and ethylacetate (4/1) as eluents afforded sequentially **12** (20 mg, 26%), the starting phosphonate **1** (30 mg, 30%), and **15** (11 mg, 11%).

15: ^{1}H NMR (90 MHz, CDCl$_3$): 6.16 (d, 1H, ^3J(PH$_{cis}$) 23.3, H7); 5.88 (d, 1H, ^3J(PH$_{trans}$) 48.2, H7); 6.0 to 5.64 (m, 2H, H3, H4); 3.80 (d, 3H, ^3J(PH) 11.0) and 3.76 (d, 3H, ^3J(PH) 11.0) (P-O*Me*); 3.69 (s, 3H, CO$_2$*Me*); 1.75 (dd, 1H, *J* 9.1; ^3J(PH) 9.1, H5); 1.28 (d, 1H, *J* 7.9, H2). ^{13}C NMR (22.5 MHz, CDCl$_3$): 208.84 (s, Fe-*C*O); 172.19 (s, *C*O$_2$Me); 137.34 (d, ^1J(CP) 181.9, C6); 125.71 (t, *J* 159.8, C7); 84.71 (d, *J* 174.6, C3); 81.52 (dd, *J* 169.2, ^3J(CP) 10.7, C4); 53.2 [m, C5 and P(O*Me*)$_2$]; 51.79 (q, *J* 147.0, CO$_2$*Me*); 46.09 (d, *J* 164.5, C2). IR (film, cm^{-1}): 2070 and 2000 (C≡O), 1720 (C=O).

Acknowledgments

We thank Professor Donaldson for sharing his results with us prior to publication and for fruitful discussions. L.S. thanks Roussel-Uclaf for a fellowship. Partial financial support from CNRS is also gratefully acknowledged.

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