

## Retinoids and Related Compounds. Part 22.<sup>1)</sup> Synthesis of $\beta$ -Ionone Analog Tricarbonyliron Complexes

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Received July 31, 1998; accepted October 26, 1998

The synthesis of  $\beta$ -ionone analog tricarbonyliron complexes was investigated. *N*-Methoxy-*N*-methyl-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propenamide (Weinreb amide), prepared from the corresponding ethyl ester and *N*,*O*-dimethylhydroxylamine hydrochloride, reacted smoothly with various organometallic reagents to afford the  $\beta$ -ionone analogs in good to excellent yields. Treatment of these compounds with dodecacarbonyltriiron afforded the corresponding tricarbonyliron complexes in high yields.

**Key words**  $\beta$ -ionone analog; tricarbonyliron complex; *N*-methoxy-*N*-methylamide; organometallic; retinoid

It is well known that  $\beta$ -ionone is a highly important compound for the synthesis of retinoids, carotenoids and related compounds.<sup>2)</sup> In addition we recently demonstrated that  $\beta$ -ionone tricarbonyliron complex (1), easily prepared from  $\beta$ -ionone and dodecacarbonyltriiron, is a significantly useful intermediate for the stereoselective synthesis of retinoids such as all-*E*-retinoic acid, 9*Z*-retinoic acid and 11*Z*-retinal.<sup>1,3)</sup> In connection with our conformational study of the chromophore in rhodopsin,<sup>4)</sup> we need 11*Z*-9-substituted retinal analogs, in which the methyl group at the 9 position in 11*Z*-retinal is displaced by other substituents. As we have recently accomplished a stereoselective synthesis of 11*Z*-retinal using  $\beta$ -ionone tricarbonyliron complexes,<sup>3)</sup>  $\beta$ -ionone analog tricarbonyliron complexes (2) are the key intermediates for the synthesis of 11*Z*-9-substituted retinals. In this paper, we describe the synthesis of  $\beta$ -ionone analog tricarbonyliron complexes (2) (Fig. 1).

### Results and Discussion

A previously reported method for the preparation of  $\beta$ -ionone analog (4) is a reaction of the carbanion of (*E*)-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propenal *S,S*-acetal (3) with electrophiles and the subsequent removal of the protecting group.<sup>5)</sup> At first, applying this methodology, we were able to obtain the  $\beta$ -ionone analogs (4a, e, f) in moderate yields by two steps. These compounds were converted to the corresponding tricarbonyliron complexes (2a, e, f) in good yields by the reaction with dodecacarbonyltriiron in benzene (Chart 1). We were able to prepare the desired compounds according to this method, however, the yields were not satisfactory and this method is impossible to apply to the aryl analogs such as a phenyl substituent. Therefore, we explored the alternative approaches for the preparation of 2.

Recently, we succeeded in converting the magnesium salt

of alcohol tricarbonyliron complex (5) to the corresponding aldehyde (6) without decomplexation by Mukaiyama's method<sup>6)</sup> using 1,1'-(azodicarbonyl)dipiperidine (7).<sup>1)</sup> Thus, the reaction of aldehyde tricarbonyliron complex (8) with Grignard reagent and subsequent oxidation by 7 was expected to give the desired product. The aldehyde tricarbonyliron complex (8) was prepared from the corresponding aldehyde<sup>7)</sup> with dodecacarbonyltriiron in 68% yield. Treatment of 8 with benzylmagnesium chloride and followed by oxidation with 7 afforded the two products (2e, 10e) in 49% and 38% yields, respectively. The structure of 2e was determined on the basis of its spectral data, which were identical with those of the sample obtained by the previous method. The IR spec-

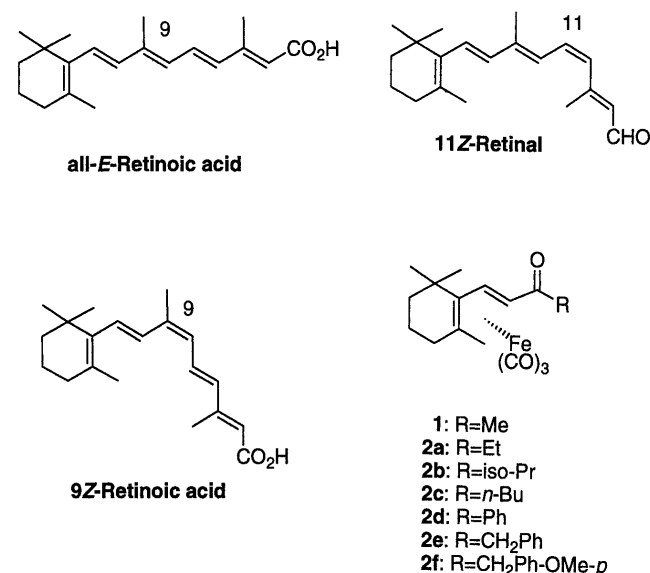


Fig. 1

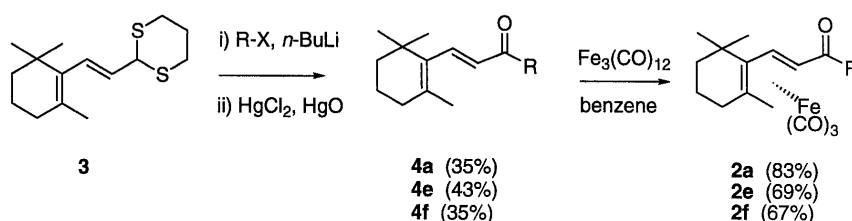


Chart 1

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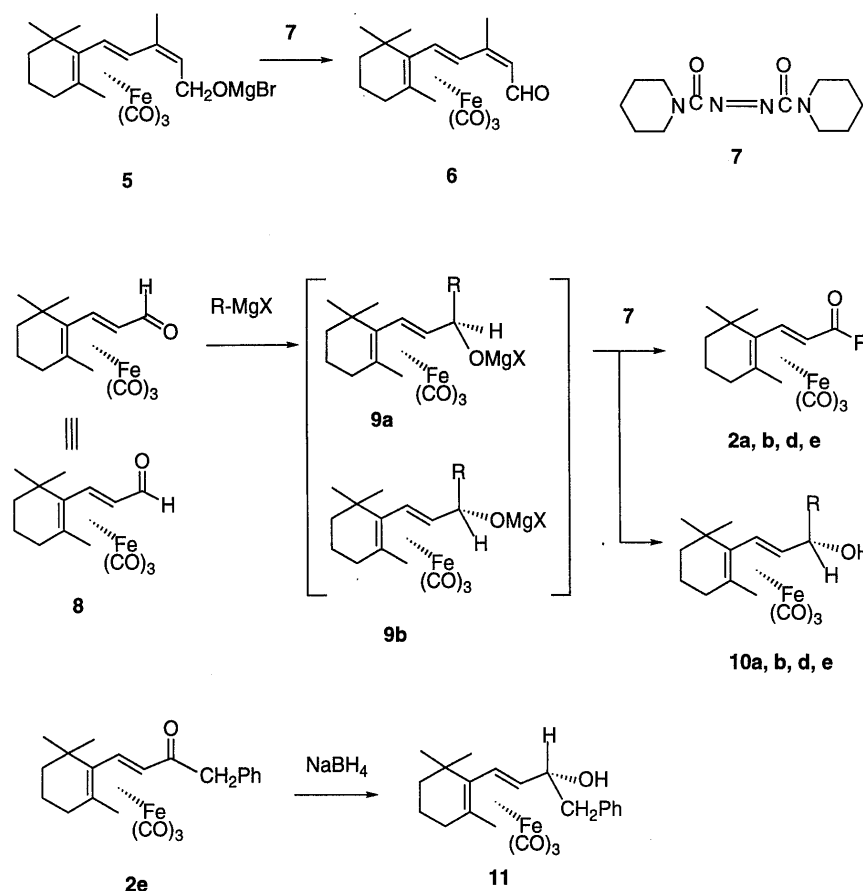


Chart 2

tra of **10e** showed an alcoholic absorption at  $3570\text{ cm}^{-1}$ , and  $^1\text{H-NMR}$  spectra exhibited benzylic methylene signals at  $\delta$  2.85 ppm (1H, dd,  $J=7, 13$  Hz) and  $\delta$  3.05 ppm (1H, dd,  $J=7, 13$  Hz). In order to establish the structure of **10e**, reduction of **2e** was performed using sodium borohydride in methanol to give an alcohol, **11**, whose NMR spectra was not identical with that of **10e**. It is known that the carbonyl group has an *s-cis* conformation in dienylketone tricarbyliron complex; therefore, the single diastereomer is produced in its reduction due to the back side attack of hydride against to the tricarbyliron.<sup>8)</sup> Consequently, from the reaction pathway, we determined these structures of **10e** and **11** as  $\psi$ -exo and  $\psi$ -endo alcohols,<sup>9)</sup> respectively.

In a similar fashion, the reactions of various Grignard reagents with **8** afforded the corresponding ketone and alcohol tricarbyliron complexes (**2**, **10**), and these results are listed in Table 1. The production of **2** and **10** is easily rationalized by consideration of the conformation of the carbonyl group in **8**. Thus, in dienylaldehyde tricarbyliron complex such as **8**, the carbonyl group had both *s-cis* and *s-trans* conformations, and the Grignard reagents approached the opposite side of tricarbyliron to give the intermediates (**9a**, **9b**), respectively. We speculated that, in intermediate **9b**, the magnesium salt of alcohol and tricarbyliron complex were placed at the same side of the plane formed by the dienal structure. In contrast, in intermediate **9a**, both functional groups were positioned opposite each other. Therefore, intermediate **9a** was easily oxidized to afford ketone tricarbyliron complexes (**2**), whereas another intermediate, **9b**, was not oxidized to give the alcohol tricarbyliron complexes

Table 1. Reaction of Tricarbyliron Complex **2** with Grignard Reagents

Run	Reagent	Products			
		Compound No.	Yield (%)	Compound No.	Yield (%)
1	EtMgBr	<b>2a</b>	34	<b>10a</b>	51
2	iso-PrMgBr	<b>2b</b>	22	<b>10b</b>	61
3	PhMgBr	<b>2d</b>	57	<b>10d</b>	21
4	PhCH <sub>2</sub> MgCl	<b>2e</b>	49	<b>10e</b>	38

(**10**) because the approach of the oxidizing reagent was disturbed by steric hindrance (Chart 2, Table 1).

The ratio of **2** and **10** seemed to depend upon the steric bulkiness of Grignard reagent. Thus, the yield of alcohol (**10**) was increased with the increase of the bulkiness of the nucleophile (iso-Pr > Et > PhCH<sub>2</sub> > Ph). This phenomenon is understood from the reaction mechanism (Fig. 2). The aldehyde complex (**8**) exists as an equilibrium between the *s-trans* (**8a**) and *s-cis* (**8b**) conformations of the carbonyl group. From consideration of the Dreiding molecular model, it is expected that the addition of the nucleophile to the carbonyl group will be much faster in conformer **8b**. Thus, in conformer **8a** the preferred angle (*ca.*  $109^\circ$ ) of the attack of the nucleophile<sup>10)</sup> is sterically hindered by one of the geminal methyl groups at the C-1 position. In contrast, in conformer **8b**, the nucleophile can approach free of such restrictions. Since the product ratios of **2** and **10** depend upon the direction of the addition of the nucleophile under the condition that the equilibrium between the conformations is rapidly established, an increase in the steric bulkiness of the nucleophile and a de-

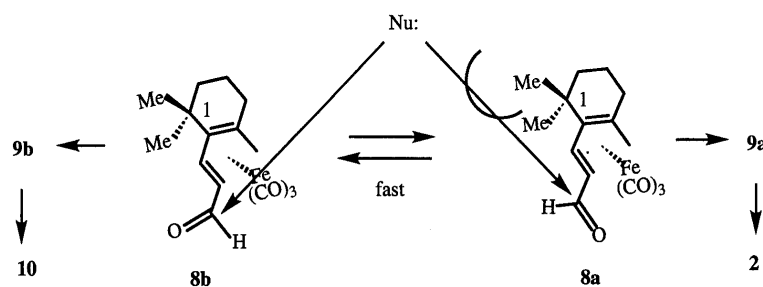


Fig. 2

crease in the desired ketone **2** derived from intermediate **9a** was observed (Fig. 2). A similar discussion has already addressed the nucleophilic addition of tricarbonylchromium complex.<sup>11</sup> All our attempts to transform **10** to the corresponding ketone **2** were unsuccessful because of the partial decomplexation under oxidative conditions.

Since Nahm and Weinreb demonstrated the convenient conversion of *N*-methoxy-*N*-methylamide to the ketone derivatives by use of organometallic reagents,<sup>12</sup> this methodology has been applied to the synthesis of various natural products.<sup>13</sup> We anticipated that the amide tricarbonyliron complex (**15**) would be a common intermediate for the preparation of various  $\beta$ -ionone analog tricarbonyliron complexes (**2**). The amide tricarbonyliron complex (**15**) was obtained from acid (**12**)<sup>7</sup> by three steps. The ethyl ester (**13**), obtained from **12** in 92% yield by the usual method using a catalytic amount of concentrated H<sub>2</sub>SO<sub>4</sub> in ethanol, was converted to the corresponding tricarbonyliron complex (**14**) by the reaction with dodecacarbonyltriiron in benzene. The ester complex (**14**) was transformed to the *N*-methoxy-*N*-methylamide (**15**) in 73% yield by treatment with *N,O*-dimethylhydroxylamine hydrochloride and diisopropylmagnesium bromide.<sup>14</sup> Treatment of **15** with benzylmagnesium chloride afforded the desired  $\beta$ -ionone analog tricarbonyliron complex (**2e**) via the reaction intermediate (**16**)<sup>12</sup> and its decomplexed compound (**4e**) in 39% and 13% yields, respectively. This result indicated that our attempt to use the amide-complex (**15**) as a common intermediate for the preparation of **2** was brought to a standstill because of the low yield of the desired product (**4**) and the occurrence of partial decomplexation under the reaction conditions. Then, we determined that the tricarbonyliron complexation step would be achieved as a final step, and the reaction of decomplexed amide (**17**) with organometallic reagents<sup>15</sup> was investigated.

The amide (**17**) was derived from the ester (**13**) in the same manner as described for the preparation of **15** in 94% yield. Treatment of the amide (**17**) with three equivalents of methyl lithium in ether at 0 °C gave the  $\beta$ -ionone (**4**; R=Me) in 56% yield. When methylmagnesium bromide was used as a nucleophile, the yield of  $\beta$ -ionone was increased to 84% yield. In a similar fashion, the reaction of the amide (**17**) with Grignard reagents or alkyl lithium reagents afforded the corresponding  $\beta$ -ionone analogs (**4**) in good to excellent yields. The results are listed in Table 2. In the case of diisopropylmagnesium bromide, the yield of **4b** was decreased due to the steric bulkiness of the reagent. The structures of these analogs were determined from the spectral data shown in Table 3. These compounds (**4**) were transformed to the corresponding tricarbonyliron complexes (**2**) by a reaction

Table 2. Reaction of Amide **17** with Organometallic Reagents

Run	Reagent	Product	Yield (%)
1	EtMgBr	<b>4a</b>	83
2	iso-PrMgBr	<b>4b</b>	35
3	<i>n</i> -BuLi	<b>4c</b>	68
4	PhLi	<b>4d</b>	65
5	PhMgBr	<b>4d</b>	69
6	PhCH <sub>2</sub> Li <sup>(a)</sup>	<b>4e</b>	73
7	PhCH <sub>2</sub> MgCl	<b>4e</b>	84

<sup>a</sup>) Prepared from toluene and *n*-BuLi in the presence of tetramethylethylenediamine.<sup>16</sup>

with dodecacarbonyltriiron in high yields (69–94%, Chart 3).

In summary, the present method described here, the reaction of the *N*-methoxy-*N*-methylamide (**17**) with organometallics, provides a novel and easy route for the synthesis of  $\beta$ -ionone analogs (**4**), and these compounds were easily converted to the corresponding tricarbonyliron complexes (**2**). The transformation of these compounds to the retinoid derivatives is under investigation in our laboratory.

#### Experimental

Boiling points are uncorrected. UV spectra were recorded on a JASCO Ubest-55 instrument and IR spectra on a Perkin-Elmer FT-IR Paragon 1000 spectrometer. <sup>1</sup>H-NMR spectra were obtained on a Varian Gemini-200 or Gemini-300 NMR spectrometer. Mass spectra were determined on a Hitachi M-4100 instrument. Column chromatography (CC) under reduced pressure by an aspirator (*ca.* 30 mmHg) was performed using Merck Silica gel 60. All reactions were carried out under a nitrogen atmosphere. Materials obtained from commercial suppliers were used without further purification except when otherwise noted. Tetrahydrofuran (THF) and ether were purified by distillation from benzophenone sodium ketyl under nitrogen. Diisopropylamine was purified by distillation from CaH<sub>2</sub>. Standard workup means that the organic layers were finally washed with brine, dried over anhydrous sodium sulfate (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* below 30 °C using a rotary evaporator.

#### General Procedure for the Preparation of $\beta$ -Ionone Analogs (**4a, e, f**)

**from the *S,S*-Acetal (**3**)** A solution of *n*-BuLi (1.6 mol hexane solution, 2.8 ml, 4.48 mmol) was added dropwise to a stirred solution of the *S,S*-acetal (**3**, 1 g, 3.73 mmol) in THF (5 ml) at 0 °C. The mixture was stirred for 30 min at room temperature, and a solution of alkyl bromide or alkyl chloride (4.48 mmol) was added at –78 °C. After stirring for an additional 30 min under the same conditions, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (5 ml) and then extracted with Et<sub>2</sub>O (50 ml × 3). The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated. To this residue, MeOH (30 ml), HgCl<sub>2</sub> (1.08 g, 4.6 mmol) and HgO (518 mg, 2.39 mmol) were added and the resulting mixture was stirred for 15 min at room temperature. After the evaporation of MeOH, the crude product was filtered off through Celite with Et<sub>2</sub>O, followed by a standard workup. The residue was purified by CC (ether : hexane = 1 : 4 as an eluent) to give the  $\beta$ -ionone analog (**4**) as a colorless oil.

(4*E*)-5-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-4-penten-3-one (**4a**): This was prepared from **3** (500 mg, 1.87 mmol) and ethyl bromide (244 mg, 2.24 mmol) in 35% yield (134 mg) as a colorless oil. This compound was identical with the authentic specimen obtained by the later method.

Table 3. Physical and Spectral Data of  $\beta$ -Ionone Analogs 4

Product	Molecular formula	UV (EtOH) $\lambda$ (nm)	IR (CHCl <sub>3</sub> ) $\nu$ (cm <sup>-1</sup> )	<sup>1</sup> H-NMR (CDCl <sub>3</sub> /TMS), $\delta$ (ppm), $J$ (Hz)
4a	C <sub>14</sub> H <sub>22</sub> O	294	2936 1660 1604	1.06 (6H, s), 1.14 (3H, t, $J=7$ ), 1.40–1.70 (4H, m), 1.76 (3H, s), 2.06 (2H, br t, $J=6$ ), 2.61 (2H, q, $J=7$ ), 6.13 (1H, d, $J=16$ ), 7.31 (1H, d, $J=16$ )
4b	C <sub>15</sub> H <sub>24</sub> O	297	2934 1682 1603	1.07 (6H, s), 1.15 (6H, d, $J=7$ ), 1.46–1.70 (4H, m), 1.77 (3H, s), 2.04–2.10 (2H, m), 2.84 (1H, sep, 1H, $J=7$ ), 6.20 (1H, d, $J=16$ ), 7.36 (1H, d, $J=16$ )
4c	C <sub>16</sub> H <sub>26</sub> O	295	3000 1681 1603	0.93 (3H, t, $J=7$ ), 1.06 (6H, s), 1.30–1.70 (8H, m), 1.75 (3H, s), 2.06 (2H, br t, $J=6$ ), 2.57 (2H, t, $J=8$ ), 6.13 (1H, d, $J=16$ ), 7.30 (1H, d, $J=16$ )
4d	C <sub>18</sub> H <sub>22</sub> O	319 256	2931 1657 1600	1.13 (6H, s), 1.35–1.75 (4H, m), 7.93 (2H, m), 1.85 (3H, s), 2.06 (2H, br t, $J=6$ ), 6.94 (1H, d, $J=16$ ), 7.41–7.62 (4H, m)
4e	C <sub>19</sub> H <sub>24</sub> O	260	2935 1675 1602	1.01 (6H, s), 1.42–1.64 (4H, m), 1.69 (3H, s), 2.05 (2H, br t, $J=6$ ), 3.87 (2H, s), 6.16 (1H, d, $J=16$ ), 7.28–7.20 (3H, m), 7.36–7.30 (2H, m), 7.37 (1H, d, $J=16$ )

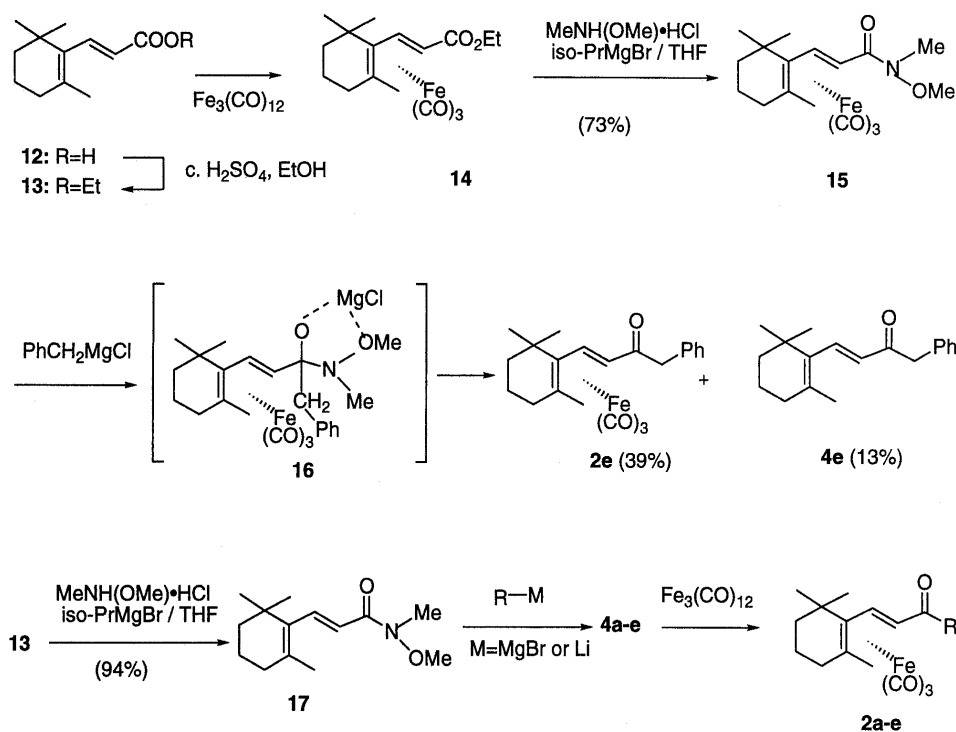


Chart 3

(3*E*)-1-Phenyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (**4e**): This was prepared from **3** (1 g, 3.73 mmol) and benzyl bromide (1.13 ml, 4.48 mmol) in 43% yield (434 mg) as a colorless oil. This compound was identical with the authentic specimen obtained by the later method.

(3*E*)-1-(4-Methoxy phenyl)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (**4f**): This was prepared from **3** (1.9 g, 7.16 mmol) and *p*-methoxybenzyl chloride (4.83 ml, 7.88 mmol) in 35% yield (580 mg) as a colorless oil. UV  $\lambda_{\text{max}}$  (EtOH) nm: 300, 224; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2936, 1679, 1610; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.01 (6H, s), 1.43–1.62 (4H, m), 1.69 (3H, s), 2.04 (2H, br t), 3.79 (5H, s), 6.15 (1H, d,  $J=16$  Hz), 6.86 (2H, d,  $J=8.5$  Hz), 7.15 (2H, d,  $J=8.5$  Hz), 7.36 (1H, d,  $J=16$  Hz); HR-MS  $m/z$ : 298.1944 (Calcd for C<sub>20</sub>H<sub>26</sub>O<sub>2</sub>: 298.1944).

Tricarbonyl[2,3,1,2- $\eta^4$ -(2*E*)-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propen-1-yl]iron(0) (**8**): A mixture of (2*E*)-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propen-1-yl (1.0 g, 5.6 mmol)<sup>7</sup> and Fe<sub>3</sub>(CO)<sub>12</sub> (3.1 g, 6.2 mmol) in benzene (50 ml) was heated under reflux for 20 h. The resulting mixture was passed the short aluminum column to remove the excess reagent, and the eluent was concentrated under reduced pressure. The residue was purified by CC (ether:hexane=1:6 as an eluent) to give the tricarbonyliron complex (**8**, 403 mg, 23%) as an orange solid. UV  $\lambda_{\text{max}}$  (EtOH)

nm: 252.5 (sh), 225; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2050, 1990, 1675; <sup>1</sup>H-NMR (200 MHz)  $\delta$ : 1.23 (3H, s), 1.42 (3H, s), 1.48 (3H, s), 1.5–1.6 (4H, m), 1.9–2.0 (2H, m), 2.41 (1H, dd,  $J=8.5$ , 4 Hz), 5.61 (1H, d,  $J=8.5$  Hz), 9.33 (1H, d,  $J=4$  Hz); HR-MS  $m/z$ : 318.0556 (Calcd for C<sub>15</sub>H<sub>18</sub>FeO<sub>4</sub>: 318.0555).

**General Procedure for the Preparation of  $\beta$ -Ionone Analog Tricarbonyliron Complexes (2a, b, d, e) from the Aldehyde Tricarbonyliron Complex (8)** A solution of Grignard reagent (4 eq, 8 mmol) was added dropwise to a stirred solution of the aldehyde (**8**, 636 mg, 2 mmol) in anhydrous Et<sub>2</sub>O (20 ml) at 0 °C, and the resulting mixture was stirred for an additional 10 min. A solution of 1,1-(azodicarbonyl)dipiperidine (**7**, 1.3 eq, 2.6 mmol) in THF (5 ml) was added at 0 °C, and the mixture was stirred for another 20 min under the same conditions. The reaction was quenched with saturated aqueous NaCl (5 ml) and extracted with Et<sub>2</sub>O (50 ml×3), followed by the standard work up. The residue was purified by CC (ether:hexane=1:9 as an eluent) to give the  $\beta$ -ionone tricarbonyliron complex analog (**2**) as a yellow oil from the first fraction and the alcohol tricarbonyliron complex (**10**) as a yellow oil from the second fraction.

Tricarbonyl[4,5,1,2- $\eta^4$ -(4*E*)-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-4-penten-3-one]iron(0) (**2a**) and Tricarbonyl[4,5,1,2- $\eta^4$ -(3*R*\*,4*R*\*,2*S*\*)-(4*E*)-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-4-penten-3-ol]iron(0) (**10a**): These (**2a**,

**10a**) were prepared from **8** (100 mg, 0.31 mmol) and EtMgBr (3 M solution, 0.31 ml, 0.94 mmol) in 34% (37 mg) and 51% (55 mg) yields, respectively. The compound **2a** was identical with the authentic specimen obtained by the later method. **10a**: UV  $\lambda_{\max}$  (EtOH) nm: 232; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2963, 2034, 1968; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.02 (3H, t, *J*=7.5 Hz), 1.14 (3H, s), 1.36 (3H, s), 1.44 (3H, s), 1.5—1.68 (7H, m), 1.78—1.95 (2H, m), 2.12 (1H, t, *J*=8 Hz), 3.28—3.31 (1H, m), 5.07 (1H, d, *J*=8 Hz); HR-MS *m/z*: 348.1025 (Calcd for C<sub>17</sub>H<sub>24</sub>FeO<sub>4</sub>: 348.1011).

Tricarbonyl[4,5,1,2- $\eta^4$ -(4*E*)-2-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-4-penten-3-one]iron(0) (**2b**) and Tricarbonyl[4,5,1,2- $\eta^4$ -(3*R*\*,4*R*\*,2*S*\*)-(4*E*)-2-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-4-penten-3-ol]iron(0) (**10b**): These (**2b**, **10b**) were prepared from **8** (318 mg, 1 mmol) and iso-PrMgBr (0.69 M solution, 1.9 ml, 1.3 mmol) in 22% (70 mg) and 61% (195 mg) yields, respectively. The compound **2b** was identical with the authentic specimen obtained by the later method. **10b**: UV  $\lambda_{\max}$  (EtOH) nm: 232; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3606, 2963, 2035, 1944; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 0.96 (3H, d, *J*=7 Hz), 1.00 (3H, d, *J*=7 Hz), 1.14 (3H, s), 1.37 (3H, s), 1.44 (3H, s), 1.47 (d, 1H, *J*=5 Hz), 1.50—1.66 (4H, m), 1.80—2.05 (3H, m), 2.18 (1H, br t, *J*=8.5 Hz), 3.30—3.37 (1H, m), 5.14 (1H, d, *J*=8.5 Hz); HR-MS *m/z*: 362.1188 (Calcd for C<sub>18</sub>H<sub>26</sub>FeO<sub>4</sub>: 362.1182).

Tricarbonyl[2,3,1,2- $\eta^4$ -(2*E*)-1-phenyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propen-1-one]iron(0) (**2d**) and Tricarbonyl[2,3,1,2- $\eta^4$ -(1*R*\*,2*R*\*,2*S*\*)-(2*E*)-1-phenyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propen-1-ol]iron(0) (**10d**): These (**2d**, **10d**) were prepared from **8** (636 mg, 2 mmol) and PhMgBr (3 M solution, 0.64 ml, 1.9 mmol) in 57% (448 mg) and 21% (168 mg) yields, respectively. The compound **2d** was identical with the authentic specimen obtained by the later method. **10d**: UV  $\lambda_{\max}$  (EtOH) nm: 243; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2933, 2037, 1972; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.17 (3H, s), 1.39 (3H, s), 1.47 (3H, s), 1.48—1.65 (4H, m), 1.84—1.86 (2H, m), 2.07 (1H, br s), 2.40 (1H, t, *J*=8 Hz), 4.43 (1H, d, *J*=8 Hz), 5.27 (1H, d, *J*=8 Hz), 7.25—7.43 (5H, m); HR-MS *m/z*: 396.1030 (Calcd for C<sub>21</sub>H<sub>24</sub>FeO<sub>4</sub>: 396.1025).

Tricarbonyl[3,4,1,2- $\eta^4$ -(3*E*)-1-phenyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one]iron(0) (**2e**) and (2*R*\*,3*R*\*,2*S*\*)-Tricarbonyl[3,4,1,2- $\eta^4$ -(3*E*)-1-phenyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-ol]iron(0) (**10e**): These (**2e**, **10e**) were prepared from **8** (636 mg, 2 mmol) and PhCH<sub>2</sub>MgCl (2 M solution, 1.17 ml, 2.4 mmol) in 49% (40 mg) and 38% (321 mg) yields, respectively. The compound **2e** was identical with the authentic specimen obtained by the later method. **10e**: UV  $\lambda_{\max}$  (EtOH) nm: 236; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3568, 2030, 1950; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.17 (3H, s), 1.36 (3H, s), 1.45 (3H, s), 1.45—1.70 (4H, m), 1.77 (1H, s), 1.90—2.05 (2H, m), 2.16 (1H, br t, *J*=8 Hz), 2.76 (1H, dd, *J*=10, 14 Hz), 3.19 (1H, dd, *J*=14, 2 Hz), 3.57 (1H, m), 5.11 (1H, d, *J*=8 Hz), 7.24—7.38 (5H, m); HR-MS *m/z*: 410.1197 (Calcd for C<sub>22</sub>H<sub>26</sub>FeO<sub>4</sub>: 410.1182).

Tricarbonyl[3,4,1,2- $\eta^4$ -(2*R*\*,3*S*\*,2*R*\*)-(3*E*)-1-phenyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-ol]iron(0) (**11**) To a stirred solution of the  $\beta$ -ionone analog-tricarbonyliron complex (**2e**, 18 mg, 0.04 mmol) in MeOH (3 ml) was added NaBH<sub>4</sub> (5.5 mg, 0.15 mmol) at 0 °C. After stirring for an additional 30 min, the reaction mixture was poured into ice water and extracted with ether (3 $\times$ 50 ml), followed by the standard workup. The residue was purified by CC on silica gel (ether:hexane=1:9 as an eluent) to give the alcohol (**11**) as a yellow oil in 25% yield (4.5 mg). UV  $\lambda_{\max}$  (EtOH) nm: 237; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3570, 2028, 1950; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.11 (3H, s), 1.22 (3H, s), 1.25 (3H, s), 1.45—1.70 (4H, m), 1.63 (1H, s), 1.78—1.98 (2H, m), 2.14 (1H, br t, *J*=9 Hz), 2.85 (1H, dd, *J*=7, 13 Hz), 3.05 (1H, dd, 1H, *J*=7, 13 Hz), 3.52 (1H, m), 4.49 (1H, d, *J*=9 Hz), 7.13—7.36 (5H, m); HR-MS *m/z*: 410.1197 (Calcd for C<sub>22</sub>H<sub>26</sub>FeO<sub>4</sub>: 410.1202).

**Ethyl (2*E*)-3-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-propenoate (13)** A mixture of carboxylic acid (**12**, 10 g, 51.5 mmol)<sup>7</sup> and a few drops of concentrated H<sub>2</sub>SO<sub>4</sub> in EtOH (40 ml) was heated under reflux for 6 h. After cooling, ethanol was removed by evaporation *in vacuo* and the residue was extracted with ether (3 $\times$ 80 ml). The combined extracts were washed with brine (30 ml), dried over (Na<sub>2</sub>SO<sub>4</sub>), then concentrated. The residue was purified by distillation to give the ester (**13**) as a colorless oil in 92% yield (10.6 g). bp: 125—128 °C (7 mmHg); IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 1702, 1613; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.06 (6H, s), 1.31 (3H, t, *J*=7 Hz), 1.45—1.49 (2H, m), 1.58—1.64 (2H, m), 1.76 (3H, s), 2.06 (2H, br t, *J*=6 Hz), 4.22 (2H, q, *J*=7 Hz), 5.82 (1H, d, 1H, *J*=16 Hz), 7.42 (1H, d, *J*=16 Hz); HR-MS *m/z*: 222.1624 (Calcd for C<sub>14</sub>H<sub>22</sub>O<sub>2</sub>: 222.1619); *Anal.* Calcd for C<sub>14</sub>H<sub>22</sub>O<sub>2</sub>: C, 75.63; H, 9.97. Found: C, 75.37; H, 10.10.

**Tricarbonyl[ethyl 2,3,1,2- $\eta^4$ -(2*E*)-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propenoate]iron(0) (14)** This was prepared from the ester (**13**, 1 g, 4.5 mmol) and Fe<sub>2</sub>(CO)<sub>9</sub> (11.3 g, 22 mol) in the same manner as described for the preparation of **2** in 97% yield (1.58 g). UV  $\lambda_{\max}$  (EtOH) nm: 236; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2934, 2047, 1986, 1669, 1602; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.16

(3H, s), 1.42 (3H, s), 1.26 (3H, t, *J*=7 Hz), 1.45 (3H, s), 1.49—1.68 (4H, m), 1.89—1.95 (2H, m), 2.15 (1H, d, *J*=8.5 Hz), 4.11 (1H, dq, *J*=11, 7 Hz), 4.16 (1H, dq, *J*=11, 7 Hz), 5.62 (1H, d, *J*=8.5 Hz); HR-MS *m/z*: 362.0829 (Calcd for C<sub>17</sub>H<sub>22</sub>FeO<sub>5</sub>: 362.0818).

**Tricarbonyl[2,3,1,2- $\eta^4$ -(2*E*)-*N*-methoxy-*N*-methyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propenamido]iron(0) (15)** To a stirred solution of the ester tricarbonyliron complex (**14**, 360 mg, 1 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (300 mg, 3 mmol) in THF (10 ml) was added dropwise iso-propylmagnesium bromide (0.67 M solution, 9 ml, 6 mmol) at -20 °C. After stirring for an additional 30 min, the reaction was quenched with saturated NH<sub>4</sub>Cl (15 ml) and the mixture was extracted with ether (3 $\times$ 20 ml). The combined extracts were washed with brine (20 ml), dried over (Na<sub>2</sub>SO<sub>4</sub>), then concentrated. The residue was purified by CC (ether:hexane=1:4) to afford the amide (**15**) as a pale yellow oil in 73% yield (271 mg). UV  $\lambda_{\max}$  (EtOH) nm: 240; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2938, 2045, 1983, 1665, 1636; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.19 (3H, s), 1.43 (3H, s), 1.46 (3H, s), 1.48—1.70 (4H, m), 1.88—1.97 (2H, m), 2.63 (1H, d, *J*=8.5 Hz), 3.18 (3H, s), 3.76 (3H, s), 5.75 (1H, d, *J*=8.5 Hz); HR-MS *m/z*: 377.0921 (Calcd for C<sub>17</sub>H<sub>23</sub>FeNO<sub>5</sub>: 377.0921).

**Reaction of the Amide Tricarbonyliron Complex (15) with Benzylmagnesium Chloride** To a solution of the amide (**15**, 234 mg, 0.6 mmol) in THF (8 ml) was added a solution of benzylmagnesium chloride (2 M solution, 0.6 ml, 1.2 mmol) at 0 °C. After stirring for an additional 30 min, the reaction was quenched with saturated NH<sub>4</sub>Cl (10 ml) and the mixture was extracted with ether (3 $\times$ 15 ml), followed by the standard workup. The residue was purified by CC on silica gel (ether:hexane=1:9 as an eluent) to give the  $\beta$ -ionone analog tricarbonyliron complex (**2e**, 72 mg, 39%) and its de-complexed product (**4e**, 22 mg, 13%), respectively. These compounds were identical with authentic specimens obtained from *S,S*-acetal (**3**) and aldehyde tricarbonyliron complex (**8**).

**(2*E*)-*N*-Methoxy-*N*-methyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propenamido (17)** To a stirred solution of the ester (**13**, 2.3 g, 10 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (1.3 g, 15 mmol) in THF (15 ml) was added dropwise iso-propylmagnesium bromide (0.67 M solution, 40 ml, 30 mmol) at -20 °C. After stirring for an additional 30 min, the reaction was quenched with saturated NH<sub>4</sub>Cl (30 ml), and the mixture was extracted with ether (3 $\times$ 50 ml). The combined extracts were washed with brine (30 ml), dried over (Na<sub>2</sub>SO<sub>4</sub>), then concentrated. The residue was purified by distillation to afford the amide (**17**) as a colorless oil in 94% yield (2.5 g). bp: 180—200 °C (9 mmHg) (bath temp.); IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 1645, 1609; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.07 (6H, s), 1.43—1.68 (4H, m), 1.77 (3H, s), 2.06 (2H, br t, *J*=6 Hz), 3.27 (3H, s), 3.71 (3H, s), 6.39 (1H, d, *J*=16 Hz), 7.43 (1H, d, *J*=16 Hz); HR-MS *m/z*: 237.1719 (Calcd for C<sub>14</sub>H<sub>23</sub>NO<sub>2</sub>: 237.1730); *Anal.* Calcd for C<sub>14</sub>H<sub>23</sub>NO<sub>2</sub>: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.72; H, 10.08; N, 5.87.

**General Procedure for Preparation of  $\beta$ -Ionone Analogs from the Amide (17)** To a solution of the amide (**17**, 710 mg, 3 mmol) in THF (18 ml) was added an organometallic reagent (3 eq, 9 mmol) at 0 °C. After stirring for an additional 30 min, the reaction was quenched with saturated NH<sub>4</sub>Cl (30 ml) and the mixture was extracted with ether (3 $\times$ 30 ml) followed by the standard workup. The residue was purified by CC on silica gel (ether:hexane=1:9 as an eluent) to give the  $\beta$ -ionone analog (**4**) as a colorless oil (Tables 2, 3).

**(4*E*)-5-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-4-penten-3-one (4a)**: This was prepared from **17** (710 mg, 3 mmol) and EtMgBr (3 M solution, 3 ml, 9 mmol) in 83% yield (500 mg). HR-MS *m/z*: 206.1690 (Calcd for C<sub>14</sub>H<sub>22</sub>O: 206.1671).

**(4*E*)-2-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-4-penten-3-one (4b)**: This was prepared from **17** (237 mg, 1 mmol) and iso-PrMgBr (0.67 M solution, 4.5 ml, 3 mmol) in 35% yield (77 mg). HR-MS *m/z*: 220.1844 (Calcd for C<sub>15</sub>H<sub>24</sub>O: 220.1828).

**(6*E*)-7-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-6-hepten-5-one (4c)**: This was prepared from **17** (112 mg, 0.47 mmol) and *n*-BuLi (1.63 M solution, 0.87 ml, 1.41 mmol) in 68% yield (75 mg). HR-MS *m/z*: 234.1989 (Calcd for C<sub>16</sub>H<sub>26</sub>O: 234.1984).

**(2*E*)-3-1-Phenyl-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propen-1-one (4d)**: i) This was prepared from **17** (106 mg, 0.45 mmol) and PhLi (1.8 M solution, 0.75 ml, 1.35 mmol) in 65% yield (74 mg). HR-MS *m/z*: 254.1640 (Calcd for C<sub>18</sub>H<sub>22</sub>O: 254.1672). ii) This was prepared from **17** (235 mg, 1 mmol) and PhMgBr (3 M solution, 1 ml, 3 mmol) in 69% yield (174 mg). This compound was identical with the authentic specimen obtained by method i).

**(3*E*)-4-1-Phenyl-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (4e)**: i) This was prepared from **17** (500 mg, 0.17 mmol) and PhCH<sub>2</sub>Li (4 mmol,

prepared by the reported method<sup>16)</sup> from *N,N*-tetramethylethylenediamine and *n*-BuLi in toluene) in 73% yield (395 mg). HR-MS *m/z*: 268.1820 (Calcd for C<sub>19</sub>H<sub>24</sub>O: 268.1823). ii) This was prepared from **17** (140 mg, 0.64 mmol) and PhCH<sub>2</sub>MgCl (2 M solution, 1 ml, 2 mmol) in 84% yield (132 mg). This compound was identical with the authentic specimen obtained by method i).

**General Procedure for the Conversion of  $\beta$ -Ionone Analogs (4a–f) to the Corresponding Tricarbonyliron Complexes (2a–f)** A mixture of  $\beta$ -ionone analog (**4**, 5 mmol) and Fe<sub>3</sub>(CO)<sub>12</sub> (3.1 g, 6 mmol) in benzene (50 ml) was heated under reflux for 20 h. The resulting mixture was passed through the short aluminum column to remove the excess reagent, and the eluent was concentrated under reduced pressure. The residue was purified by CC (ether : hexane = 1 : 6 as an eluent) to give the tricarbonyliron complex (**2**) as an orange solid.

Tricarbonyl[4,5,1,2- $\eta^4$ -(4E)-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-4-penten-3-one]iron(0) (**2a**): This was prepared from **4a** (1.24 g, 6.0 mmol) and Fe<sub>3</sub>(CO)<sub>12</sub> (4.55 g, 9.0 mmol) in 83% yield (1.73 g). UV  $\lambda_{\max}$  (EtOH) nm: 250; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2047, 1986, 1965 (sh), 1673; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.12 (3H, t, *J*=7.5 Hz), 1.21 (3H, s), 1.41 (3H, s), 1.45 (3H, s), 1.5–1.68 (4H, m), 1.90–1.96 (2H, m), 2.39 (1H, d, *J*=9 Hz), 2.45 (2H, q, *J*=7 Hz), 5.68 (1H, d, *J*=9 Hz); HR-MS *m/z*: 346.0868 (Calcd for C<sub>17</sub>H<sub>22</sub>FeO<sub>4</sub>: 346.0868).

Tricarbonyl[4,5,1,2- $\eta^4$ -(4E)-2-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-4-penten-3-one]iron(0) (**2b**): This was prepared from **4b** (758 mg, 3.45 mmol) and Fe<sub>3</sub>(CO)<sub>12</sub> (5.2 g, 10.3 mmol) in 82% yield (1.02 g). UV  $\lambda_{\max}$  (EtOH) nm: 260; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2966, 2047, 1974, 1670; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.13 (3H, d, *J*=7 Hz), 1.18 (3H, d, *J*=7 Hz), 1.22 (3H, s), 1.42 (3H, s), 1.46 (3H, s), 1.50–1.70 (4H, m), 1.85–1.97 (2H, m), 2.41 (1H, d, *J*=8.5 Hz), 2.63 (1H, sept, *J*=7 Hz), 5.68 (1H, d, *J*=8.5 Hz); HR-MS *m/z*: 360.1042 (Calcd for C<sub>18</sub>H<sub>24</sub>FeO<sub>4</sub>: 360.1025).

Tricarbonyl[6,7,1,2- $\eta^4$ -(6E)-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-6-hepten-5-one]iron(0) (**2c**): This was prepared from **4c** (0.72 g, 3.1 mmol) and Fe<sub>3</sub>(CO)<sub>12</sub> (3.1 g, 6.1 mmol) in 66% yield (0.76 g). UV  $\lambda_{\max}$  (EtOH) nm: 258; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2961, 2047, 1986, 1670; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 0.93 (3H, t, *J*=7 Hz), 1.21 (3H, s), 1.28–1.50 (H, m), 1.41 (3H, s), 1.45 (3H, s), 1.51–1.70 (6H, m), 1.89–1.96 (2H, m), 2.38 (1H, d, *J*=9 Hz), 2.40–2.50 (2H, m), 5.67 (1H, d, *J*=9 Hz); HR-MS *m/z*: 374.1197 (Calcd for C<sub>19</sub>H<sub>26</sub>FeO<sub>4</sub>: 374.1179).

Tricarbonyl[2,3,1,2- $\eta^4$ -(2E)-1-phenyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-propen-1-one]iron(0) (**2d**): This was prepared from **4d** (173 mg, 0.68 mmol) and Fe<sub>3</sub>(CO)<sub>12</sub> (516 mg, 1.0 mmol) in 79% yield (212 mg). UV  $\lambda_{\max}$  (EtOH) nm: 261; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2936, 2047, 1986, 1646; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.36 (3H, s), 1.48 (3H, s), 1.50 (3H, s), 1.52–1.70 (4H, m), 1.94–2.20 (2H, m), 3.10 (1H, d, *J*=8 Hz), 5.96 (1H, d, *J*=8 Hz), 7.46 (2H, t, *J*=7 Hz), 7.56 (1H, t, *J*=7 Hz), 7.95 (2H, d, *J*=7 Hz); HR-MS *m/z*: 394.0853 (Calcd for C<sub>21</sub>H<sub>22</sub>FeO<sub>4</sub>: 394.0868).

Tricarbonyl[3,4,1,2- $\eta^4$ -(3E)-1-phenyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one]iron(0) (**2e**): This was prepared from **4e** (477 mg, 1.78 mmol) and Fe<sub>3</sub>(CO)<sub>12</sub> (1.11 g, 2.14 mmol) in 69% yield (498 mg). UV  $\lambda_{\max}$  (EtOH) nm: 260 (sh); IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2933, 2047, 1987, 1668; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.04 (3H, s), 1.40 (3H, s), 1.42 (3H, s), 1.45–1.70 (4H, m), 1.80–1.92 (2H, m), 2.34 (1H, d, *J*=8.5 Hz), 3.67 (2H, s), 5.64 (1H, d, *J*=8.5 Hz), 7.24–7.36 (5H, m); HR-MS *m/z*: 408.1036 (Calcd for C<sub>22</sub>H<sub>24</sub>FeO<sub>4</sub>: 408.1025).

Tricarbonyl[3,4,1,2- $\eta^4$ -(3E)-1-(4-methoxy phenyl)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one]iron(0) (**2f**): This was prepared from **4f** (514 mg, 1.73 mmol) and Fe<sub>3</sub>(CO)<sub>12</sub> (1.3 g, 2.3 mmol) in 94% yield (713 mg). UV  $\lambda_{\max}$  (EtOH) nm: 258, 226; IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 2693, 2047, 1986, 1668, 1611; <sup>1</sup>H-NMR (300 MHz)  $\delta$ : 1.05 (3H, s), 1.39 (3H, s), 1.41 (3H, s), 1.49–1.62 (5H, m), 1.83–1.90 (2H, m), 3.61 (2H, s), 3.80 (3H, s), 5.64 (1H, d, *J*=8.5 Hz), 6.88 (2H, d, *J*=8.5 Hz), 7.17 (2H, d, *J*=8.5 Hz); HR-MS *m/z*: 438.1156 (Calcd for C<sub>23</sub>H<sub>26</sub>FeO<sub>5</sub>: 438.1128).

**Acknowledgments** This work was supported in part by the Ciba-Geigy Foundation (Japan) for the Promotion of Science, a Grant-in-Aid for Scientific Research (C, No. 09672292) from the Ministry of Education, Science and Culture (Japan) and the Sasakawa Scientific Research Grant from The Japan Science Society.

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