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Attachment of IR-active organometallic probe groups to flavonoid inducers of nod gene expression

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Abstract

Direct reaction of flavanones with electrophilic tricarbonyl[(1,2,3,4,5-η)cyclohexadienyliron(1 +) complexes affords organometallic derivatives for use as probes of molecular recognition events during the induction of nodulation genes in *Rhizobium leguminosarum*. A more selective preparation method has been developed by deprotonation of the flavanone prior to the addition of the cyclohexadienyliron complex.

Keywords: Organometalcarbonyl probes; Flavonoids; FTIR; *Rhizobium*; Root nodulation

1. Introduction

Organometalcarbonyl probe groups offer new opportunities to explore the mode of action of biological systems. Two recent developments have opened the way for the general application of these methods. In Paris, the Jaouen research group has established procedures for the carbonylmetalloimunoassay (CMIA) method [1], which exploits the exceptionally low detection limits (by FT-IR spectroscopy) of vibrational modes of carbonylmetal complexes, while in Norwich, the interpretation of shifts in the vibrational frequencies of these bands in solution has been studied [2], and methods for the detection of protein-bound organometalcarbonyl complexes have been demonstrated [3]. There are now several examples of the attachment of organometalcarbonyl probes to bioactive peptides [4] and oligonucleotides [5], following the initial investigations of the organometallic oestradiol derivatives some years ago by Jaouen [6].

In Norwich, our main objective is to deliver the organometalcarbonyl bioprobe to its protein binding site by attachment to a bioactive substance, and to study the binding process in solution by exploiting the environment-induced shifts in the vibrational modes in IR spectra. This frequency-shift information can give a qualitative guide to the polarity of the environment of the probe, and (by polyclonal antibody analysis of normalised antisymmetric vibrational bands [2]) the contribution of several factors to the overall polarity can be estimated. With more specialised probes, local pH [7], or the π-stacking of aromatic rings [8], can be assessed. Furthermore, we are able to detect small quantities [3] of a protein-bound organometalcarbonyl probe in the presence of a substantial excess of the unbound probe molecule.

In this paper we present results from a programme of combined synthetic and biological studies in which we will apply these methods to the examination of the molecular details of the control of nod gene induction in *Rhizobium leguminosarum*, in the early stages of the processes that lead to root nodulation and nitrogen fixation in legumes. Detailed genetic investigations have established [9] that the *Rhizobium* gene product NodD is essential for chemical signalling between legume roots and the bacteria, and that flavonoid molecules are active as inducers of nod gene expression. This has led to the proposal that the binding of plant-derived flavonoids to NodD is a key step in the signalling

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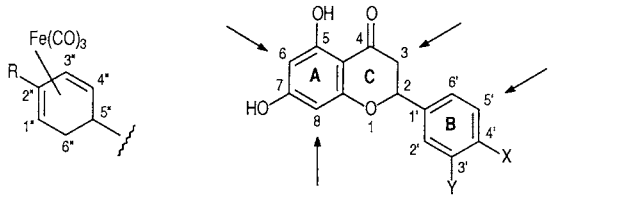


IR-active organometallic probe group
R = H,OMe

Biologically active flavanones
Naringenin **6**: X = OH, Y = H
Hesperetin **19**: X = OMe, Y = OH
Eriodictiol: X = Y = OH
(arrows indicate target sites for attachment of probe)

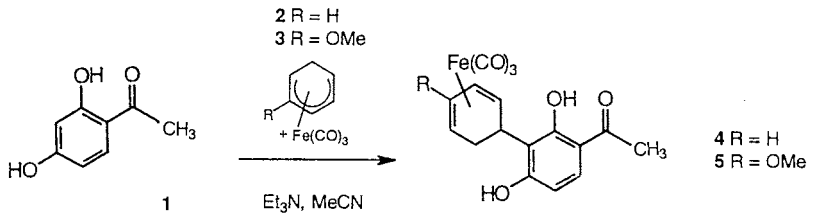
Fig. 1. Examples of flavanones with nodulation gene induction activity: sites for the attachment of organometalcarbonyl spectroscopic probes.

process. By delivery of a flavonoid-bound organometalcarbonyl probe to the NodD receptor site, we plan first to prove that binding occurs, and then examine qualitatively the local environment of the binding pocket by interpretation of the environment-induced frequency shifts. These spectroscopic experiments await the completion of model studies with crystallographically characterised protein receptors and other guest molecules. We report here, however, the results of our first attempts to synthesise organometallic derivatives of flavonoids, which have made available a representative set of compounds for biological evaluation. For success, general methods are needed for the attachment organometallic complexes to flavonoids, and the resulting derivatives must retain some measure of nod gene induction activity, so demonstrating the continued capacity to enter protein binding site despite the bulk of the attached group. Part of this work has been the subject of a preliminary communication [10].

At the start of these investigations, no examples of organometallic flavonoid derivatives had been reported. Our studies require the attachment of the probe to each of the A, B and C rings (Fig. 1) of a series of biologically active flavonoids. For ring A derivatives, a direct addition approach is possible, since the oxygenation needed here for gene induction activity should also render the ring nucleophilic, permitting direct derivatisation by reaction with electrophilic η^5-cyclohexadienyliron complexes. This would be expected to give rise to mixtures of regioisomers, but since at this stage we require only sufficient product for the bio-assay experiment, the approach is attractive provided the isomeric derivatives can be separated and identified.

2. Results and discussion

As a model to test the feasibility of this approach, 2,4-dihydroxyacetophenone (**1**) was chosen (Scheme 1) for use in reactions with the cationic η^5-cyclohexadienyliron complexes **2** and **3**. In our first experiments, a 1:1 stoichiometry of nucleophile and electrophile was employed in acetonitrile in the presence of triethylamine as a basic catalyst. The two expected products **4** and **5** (Table 1, entries 1 and 3) were obtained, but in poor yield. Repetition with an excess of salt **2** (two equivalents) improved the yield of **4** to 54% (entry 2). In the nucleophile **1**, the activating effect of the two phenolic substituents on the aromatic ring is offset by the deactivating influence of the carbonyl group of the methyl ketone. Despite this potential problem, through the use of an excess of the electrophile, successful alkylation of the aromatic ring was possible. Compared to 2,4-dihydroxyacetophone, the A ring of the commercially available flavanone naringenin **6** should be more reactive, since an additional oxygen substituent (the oxygen link in ring C) is present. The B ring is also activated as a nucleophile by an OH group, but it was hoped that the high level of oxygenation of ring A would lead to selective alkylation at this position. Based on the model study, two equivalents of the dienyl complexes were employed (Table 1, entries 4 and 6). Organometallic flavonoid derivatives were successfully obtained by this procedure (32 and 46% yield) but examination of their NMR spectra indicated that in both cases, no A ring protons were present in the region 5.7–5.9 ppm. This suggested that both nucleophilic sites on the A ring had been alkylated (Scheme 2). This possibility was confirmed by FAB mass spectrometry, which indicated MH^+ ions with masses 709 and 769, corresponding to the bimetallic products **11** and **12**, respectively. After careful chromatographic purification, the identity of these products was eventually confirmed by microanalysis in the case of **11** and high-resolution mass spectrometry in the case of **12**. From these results, it was clear that the additional activation at ring A in **6** was sufficient to make control



Scheme 1.

Table 1
Product distribution in the reaction of 2,4-dihydroxyacetophenone (**1**), naringenin (**6**), and hesperitin (**19**) with organoiron complexes **2** and **3**

Entry	Nucleophile	Electrophile			Products					
		Struct.	Subst. R	Equiv.	C-6 [a]		C-8 [a]		C-6,8 [a]	
					Struct.	Yield, %	Struct.	Yield, %	Struct.	Yield, %
1	**1**	**2**	H	1	**4**	19	–	–	–	–
2	**1**	**2**	H	2	**4**	54	–	–	–	–
3	**1**	**3**	OCH_3	1	**5**	28	–	–	–	–
4	**6**	**2**	H	2	–	–	–	–	**11**	32
5 [b]	**6**	**2**	H	1	**7**	14	**9**	2	**11**	13
6	**6**	**3**	OCH_3	2	–	–	–	–	**12**	46
7 [b]	**6**	**3**	OCH_3	1	**8**	3	**10**	Trace	**12**	4
8	**19**	**2**	H	2	–	–	–	–	**17**	28
9	**19**	**2**	H	1	**13**	11	**15**	5	**17**	5
10	**19**	**3**	OCH_3	2	–	–	–	–	**18**	25
11	**19**	**3**	OCH_3	1	**14**	15	**16**	3	**18**	9
12	**6** [c]	**2**	H	1	**7**	88	–	–	–	–

[a] Numbering system for flavanones, in the case of 2,4-dihydroxyacetophenone the organoiron complex was attached to C-3 of the aromatic ring.
[b] Starting flavanone was recovered: entry 5; 1–4%, entry 7; 27–35%.
[c] NaH before addition of **2**.

favouring monoalkylation difficult in the presence of an excess of the electrophile, but that, as expected, ring A was far more reactive than ring B. Alkylation of **6** was repeated in each case, with one equivalent of the electrophile. In the case of the electrophile **2**, two major iron-containing products were obtained under these revised conditions. Attempts at chromatographic separation of these two materials revealed a third, minor metal-containing component in the product mixture. In this way, in addition to the double adduct **11**, two further organometallic flavonoid derivatives (**7** and **9**) were obtained. The minor product **9**, however, was isolated in only 2% yield. Overall, the combined yield of the organometallic flavonoid derivatives (29%) was comparable to the yield of the double adduct when an excess of the electrophile was employed. Turning to salt **3** (entry 7), alkylation of the flavanone with a 1:1 ratio of reactants, proved much less efficient. The methoxy-substituted cyclohexadienyl complex **3** is known [11] to be significantly less reactive than its unsubstituted counterpart **2**. Despite this difficulty, sufficient material for biological testing could be obtained, even in this case. At this stage, attention turned to the flavonoid hesperetin **19**, which was prepared by hydrolysis of the commercially available hesperedin [12]. Despite the additional oxygenation on ring B, selective reaction with the dienyl complexes **2** and **3** at the A ring was still observed, and similar results were obtained. With two equivalents of the electrophiles, (Table 1, entries 8 and 10) the double adducts **17** and **18** were the only metal-containing products identified. Under the 1:1 protocol (entries 9 and 11) mixtures of **13**, **15**, **17** and **14**, **16**, **18** were produced in a fashion analogous to the results obtained with naringenin, except that the reactions with the less electrophilic salt **3** worked better in this case. In both entries 9 and 11, significantly less double alkylation was observed.

These results demonstrate that the flavanone nucleophiles naringenin **6** and hesperetin **19** can be selectively alkylated by tricarbonyliron complexes at ring A, and that both nucleophilic sites on the A ring are capable of participating in this reaction, though to different extents. In each case, one of the mono adducts was formed in considerably larger amounts than the other. Since these reactions are expected to be irreversible under these conditions, this reflects a kinetic selectivity between C-6 and C-8. Because reaction of the prochiral salt **2** and the racemic salt **3** with the chiral flavanones naringenin and hesperetin produces inseparable diastereoisomeric products[2], the NMR spectra of the adducts, particularly the double adducts, were complicated by the presence of overlapping signals, and in many cases the characteristic coupling patterns associated with 3″-H of 2″-OMe-cyclohexadieneiron complexes (coupling of 3″-H to 1″-H and 4″-H) and 2-H of the flavanone ring system (coupling of 2-H to 3α-H and 3β-H) were obscured. However, in each of the mono-adducts **7**–**10** and **13**–**16**, the remaining A-ring hydrogens appeared as the expected singlets at 5.9 or 5.7 ppm. In the case of **7**, two-dimensional NMR studies were undertaken to identify the site of alkylation and on this basis, the structures of all four kinetically favoured monoadducts were assigned as the result of reaction at C-6 of flavanone.

[2] Biological testing was performed (see ref. [10]) on single regioisomers as mixtures of diastereoisomers.

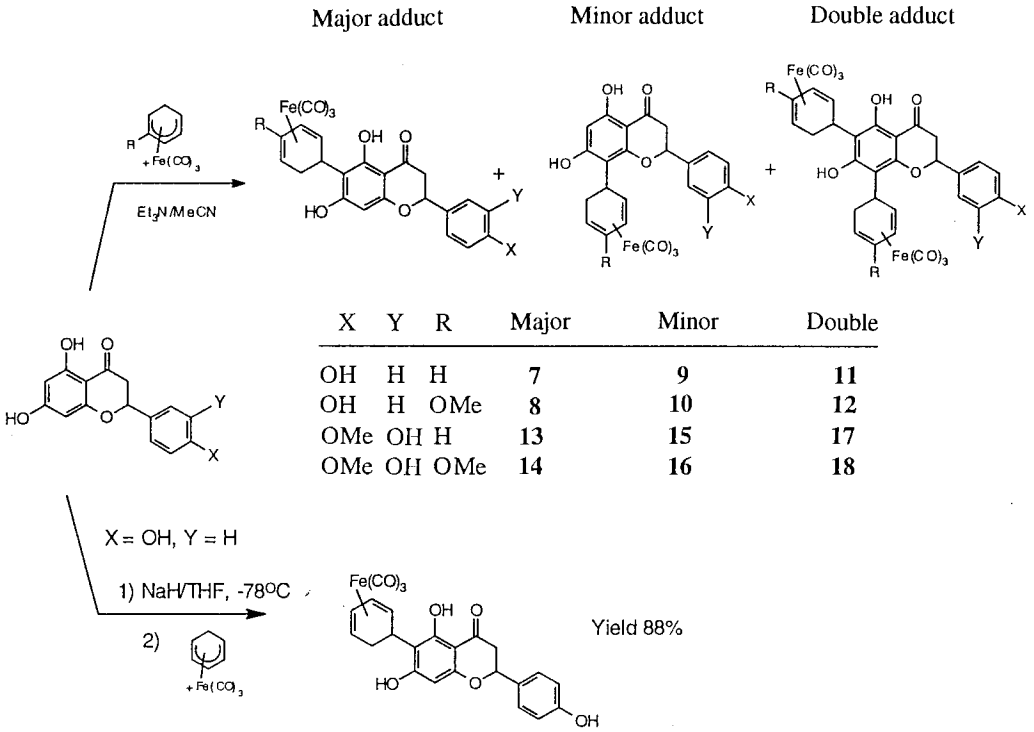
To improve the efficiency of production of the monoadducts, complete deprotonation of the phenolic OH groups with sodium hydride, prior to the addition of the electrophilic dienyl complex, was attempted. In this way, starting from naringenin **6**, efficient and selective production of the kinetically favoured monoadduct **7** was achieved in 88% yield (Scheme 2). It seems probable that efficient formation of products **8**, **13** and **14** in this way would also be possible, but since the non-selective triethylamine-catalysed process had provided sufficient of each of these compounds for biological evaluation, these reactions were not repeated using the sodium hydride procedure. Furthermore, the only route available to the minor C-8 adducts, **9**, **10**, **15** and **16** was through the use of the triethylamine-catalysed procedure on a relatively large scale, followed by extensive chromatographic purification, so the major products of the reactions were available at this stage in relatively large amounts. In the course of this work, a complete set of double adducts, **11**, **12**, **17** and **18** were also obtained, so all three possible substitution patterns at the A ring were made available for biological evaluation.

3. Conclusions

For efficient monosubstitution at C-6, the use of sodium hydride and one equivalent of the cyclohexadienyl complex is the preferred method, while with triethylamine as catalyst and an excess of the electrophile, double adducts can also be selectively obtained. The 1:1 stoichiometry, however, is the only way to prepare the C-8 regioisomer, but difficult and time-consuming chromatography is necessary to obtain a pure sample. The results of biological evaluation in an established screen for nodulation gene induction have been reported elsewhere [10], and show that the derivative **8** exhibits significant residual biological activity (510 ± 160 units at 20 μM, compared to 4500 units for eriodictiol (Fig. 1)). The derivative **8**, however, was inactive at 2 μM, while eriodictiol retains its activity at this concentration. None of the double adducts **11**, **12**, **17** or **18** was active even at 20 μM. The presence of a single organoiron-bound ring, of the correct type and in the correct situation, appears still to permit some degree of interaction of the product with its natural biological binding site, but attachment of two additional rings prevents binding.

4. Experimental

All reactions were performed under an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware twice evacuated and filled with nitrogen. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use as follows: tetrahydrofuran (THF) from sodium–benzophenone; acetonitrile from calcium hydride. Column chromatography was



X	Y	R	Major	Minor	Double
OH	H	H	**7**	**9**	**11**
OH	H	OMe	**8**	**10**	**12**
OMe	OH	H	**13**	**15**	**17**
OMe	OH	OMe	**14**	**16**	**18**

Scheme 2. Direct attachment of tricarbonyliron complexes to the A ring of flavanones.

performed using Merck silica gel. Low-resolution EI mass spectrometry (Kratos MS25) and elemental analyses were performed at the University of East Anglia by A.W.R. Saunders. Other mass spectra were measured at the EPSRC National Mass Spectrometry Service Centre, Swansea. IR spectra were recorded on a Perkin–Elmer 1720X FT-IR spectrometer. NMR spectra were recorded on a Jeol GX400 spectrometer.

4.1. General procedure for the reaction of tricarbonyl-(η^5-cyclohexadienyl)iron hexafluorophosphate salts with flavonoid compounds and 2,4-dihydroxyacetophenone

To a stirred solution at room temperature (r.t.) of the appropriate phenolic compound in dry acetonitrile were successively added triethylamine (from a small graduated syringe) and the tricarbonyl[(1,2,3,4,5-η)cyclohexadienyl]iron salt **2** or **3** (approximately one or two equivalents, see below). The progress of the reaction was followed by monitoring the disappearance of ν(CO) bands of the cation by FT-IR spectroscopy. After the salt has been consumed (usually 0.5 h), the reaction mixture was extracted with diethyl ether (50 ml). The extract was washed with water (2 × 20 ml) and brine (20 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product. Purification was performed by column chromatography on silica gel (eluent petrol ether–diethyl ether) or preparative HPLC (Dynamax C-18 column with gradient elution with methanol–water at a flow rate of 1.5 ml min^{-1}).

4.1.1. Tricarbonyl{[(1,2,3,4-η)-5α-(3′-ethanoyl-2′,6′-dihydroxyphenyl)]-1,3-cyclohexadiene}iron(0) (4)

By the general procedure, tricarbonyl[(1,2,3,4,5-η)cyclohexadienyl]iron(1 +) hexafluorophosphate(1 −) (**2**) (0.364 g, 1 mmol) was reacted with 2,4-dihydroxyacetophenone (0.152 g, 1 mmol) and triethylamine (0.16 ml, 1.1 mmol) in acetonitrile (6 ml) to afford tricarbonyl{[(1,2,3,4-η)-5α-(3′-ethanoyl-2′,6′-dihydroxyphenyl)]-1,3-cyclohexadiene}iron(0) (**4**) (0.0705 g, 19%). Similarly tricarbonyl[(1,2,3,4,5-η)cyclohexadienyl]iron (1 +) hexafluorophosphate(1 −) (0.364 g, 1 mmol) was reacted with 2,4-dihydroxyacetophenone (0.0761 g, 0.5 mmol) and triethylamine (0.16 ml, 1.1 mmol) in acetonitrile (6 ml) to afford tricarbonyl{[(1,2,3,4-η)-5α-(3′-ethanoyl-2′,6′-dihydroxyphenyl)]-1,3-cyclohexadiene}iron(0) as a pink–yellow solid (0.100 g, 54%). M.p. 169–171°C (dec.). IR ($CHCl_3$): ν_{max} 2053, 1973 (FeCO), 1631 (C=O) cm^{-1}. MS (EI) m/z (rel. int. %): 342 ($M^+ - CO$, 1), 314 ($M^+ - 2CO$, 24), 286 ($M^+ - 3CO$, 19), 284 (31), 268 (18), 266 (24), 229 (16), 213 (24), 137 (18), 115 (12), 78 (78). Anal. Calc. for $C_{17}H_{14}O_6Fe$: C, 55.14; H, 3.78. Found: C, 55.1; H, 3.8%. NMR, ^{1}H: δ (400 MHz, $CDCl_3$) 1.82 (d, J 11 Hz, 1H, 6α-H), 2.18 (m, 1H, 6β-H), 2.54 (s, 3H, COMe), 3.04 and 3.27 (2 × m, 2 × 1H; 1,4-H), 4.09 (m, 1H; 5β-H), 5.44 and 5.56 (2 × m, 2 × 1H; 2,3-H), 5.69 (s, 1H, C′6-OH), 6.30 (d, J 9 Hz, 1H, 5′-H), 7.50 (d, J 9 Hz, 1H, 4′-H), 13.20 (s, 1H, C′2-OH). ^{13}C: δ (100 MHz, $CDCl_3$) 211 (FeCO), 203 (C=O), 163 and 160 (2′,4′C), 130 (5′-C or 6′C), 117 and 114 (1′,3′C), 108 (5′-C or 6′C), 85 (2,3-C, superimposed), 64.2 and 60 (1,4-C), 32 (5-C), 27 (6-C), 26 (Me).

4.1.2. Tricarbonyl{[(1,2,3,4-η)-2-methoxy-5α-(3′-ethanoyl-2′,6′-dihydroxyphenyl)]-1,3-cyclohexadiene}iron(0) (5)

By the general procedure, tricarbonyl[(1,2,3,4,5-η)-2-methoxycyclohexadienyl]iron(1 +) hexafluorophosphate(1 −) (**3**) (0.394 g, 1 mmol) was reacted with 2,4-dihydroxyacetophenone (0.0761 g, 0.5 mmol) and triethylamine (0.16 ml, 1.1 mmol) in acetonitrile (6 ml) to afford tricarbonyl{[(1,2,3,4-η)-2-methoxy-5α-(3′-ethanoyl-2′,6′-dihydroxyphenyl)]-1,3-cyclohexadiene}-iron(0) (**5**) as a dark viscous golden oil (0.055 g, 28%). IR ($CHCl_3$): ν_{max} 2044, 1969 (FeCO), 1621 (CO) cm^{-1}. MS (EI) m/z (rel. int. %): 344 ($M^+ - 2CO$, 13), 314 (20), 260 (25), 213 (27), 137 (30), 108 (98), 78 (65). Anal. Calc. for $C_{18}H_{16}O_7Fe$: C, 54.03; H, 4.03. Found: C, 54.3; H, 4.2%. NMR, ^{1}H: δ (400 MHz, $CDC1_3$) 2.02 (d, J 14 Hz, 1H, 6α-H), 2.16 (m, 1H, 6β-H), 2.54 (s, 3H, COMe), 2.61 (m, 1H, 4-H), 3.47 (m, 1H, 1-H), 3.69 (s, 3H, OMe), 3.81 (dm, J 8.0 Hz, 1H, 5β-H), 5.15 (m, 1H, 3-H), 6.29 (d, J 8.0 Hz, 1H, 5′-H), 7.50 (d, J 8.0 Hz, 1H, 4′-H).

4.1.3. 4′,5,7-Trihydroxy-6-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (7), 4′,5,7-trihydroxy-8-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (9) and 4′,5,7-trihydroxy-6,8-bis-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (11)

By the general procedure, tricarbonyl[(1,2,3,4,5-η)cyclohexadienyl]iron(1 +) hexafluorophosphate(1 −) (**2**) (0.363 g, 1 mmol) was reacted with 4′,5,7-trihydroxyflavanone (0.272 g, 1 mmol) and triethylamine (0.42 ml, 2.9 mmol) in acetonitrile (10 ml) to afford 4′,5,7-trihydroxy-6-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**7**) (0.07 g, 14%), 4′,5,7-trihydroxy-8-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**9**) (0.0105 g, 2%) and 4′,5,7-trihydroxy-6,8-bis-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**11**) (0.0917 g, 13%) as dark viscous golden oils. Similarly, tricarbonyl[(1,2,3,4,5-η)cyclohexadienyl]iron(1 +) hexafluorophosphate(1 −) (0.400 g, 1.1 mmol) was reacted with 4′,5,7-trihydroxyflavanone (0.136 g, 0.5 mmol) and triethylamine (2.2 ml, 1.5 mmol) in acetonitrile (10 ml) to afford 4′,5,7-trihydroxy-6,8-bis-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**11**) (0.125 g, 32%).

4′,5,7-Trihydroxy-6-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**7**). IR ($CHCl_3$): ν_{max} 2053, 2040, 1973 (FeCO), 1636 (C=O) cm^{-1}. MS (FAB) m/z (rel. int. %): 491 (MH^+, 50), 434 (M^+

−2CO, 100), 406 ($M^+ - 3CO$, 80), 391 (17), 362 (17), 285 (22). Anal. Calc. for $C_{24}H_{18}O_8Fe$: C, 58.78; H, 3.67. Found: C, 58.4; H, 3.8%. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.81 (m, 1H, 6″α-H), 2.10 (m, 1H, 6″β-H), 2.98 (m, 1H, 3α-H), 3.00–3.22 (m, 3 × 1H; 1″,3β, 4″-H); 3.93 (m, 1H, 5″β-H); 5.27 (m, 1H, 2-H); 5.39 and 5.53 (2 × m, 2 × 1H; 2″,3″-H), 5.92 (s, 1H, 8-H), 6.94 (d, *J* 6.0 Hz, 2H; 3′,5′-H), 7.32 (d, *J* 6.0 Hz, 2H; 2′,6′-H); 12.50 (s, 1H, 5-OH).

4′,5,7-Trihydroxy-8-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**9**). IR ($CHCl_3$): ν_{max} 2051, 2041, 1973 (FeCO), 1632 (C=O) cm^{-1}. MS (FAB) *m*/*z* (rel. int. %): 491 (MH^+, 2), 447 (23), 391 (100), 362 (17), 289 (16), 279 (52). HRMS (FAB) Calc. for $C_{24}H_{19}O_8Fe$ (MH^+), 491.0429. Found: 491.0429. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.81 (m, 1H, 6″α-H), 2.20 (m, 1H, 6″β-H), 2.76 (m, 1H, 3α-H), 2.92–3.23 (m, 4 × 1H; 1″,3β,4″,5″β-H); 5.30 (m, 1H, 2-H); 5.46 and 5.52 (2 × m, 2 × 1H; 2″,3″-H), 5.90 (s, 1H, 6-H), 6.88 (d, *J* 6.0 Hz, 2H; 3′,5′-H), 7.31 (d, *J* 6.0 Hz, 2H; 2′,6′-H); 12.54 (s, 1H, 5-OH).

4′,5,7-Trihydroxy-6,8-bis-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**11**). IR ($CHCl_3$): ν_{max} 2053, 2041, 1974 (FeCO), 1623 (C=O) cm^{-1}. MS (FAB) *m*/*z* (rel. int. %): 709 (MH^+, 42), 652 ($M^+ - 2CO$, 85), 624 ($M^+ - 3CO$, 100), 556 (70), 536 (30), 362 (45), 219 (35), 136 (37). Anal. Calc. for $C_{33}H_{24}O_{11}Fe_2$: C, 55.93; H, 3.39. Found: C, 55.8; H, 3.2%. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.57–1.77 (m, 2 × 1H, 6″α-H), 2.08 and 2.21 (2 × m, 2 × 1H, 6″β-H), 2.77 (m, 1H, 3α-H), 2.85–3.26 (m, 5 × 1H; 1″,4″- and 3β-H); 3.91 and 4.03 (2 × m, 2 × 1H, 5″β-H); 4.97–5.11 (m, 3 × 1H; 2 and 3″-H), 5.47 and 5.67 (2 × m, 2 × 1H; 2″-H); 6.92 (d, *J* 7.0 Hz, 2H; 3′,5′-H), 7.33 (d, *J* 7.0 Hz, 2H; 2′,6′-H); 12.58 (s, 1H, 5-OH).

*4.1.4. 4′,5,7-Trihydroxy-6-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-ylliron(0)}flavanone (**8**), 4′,5,7-trihydroxy-8-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}-flavanone (**10**), and 4′,5,7-trihydroxy-6,8-bis-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**12**)*

By the general procedure, tricarbonyl[(1,2,3,4,5-η)-2-methoxycyclohexadienyl]iron(1 +) hexafluorophosphate(1 −) (**3**) (0.394 g, 1 mmol) was reacted with 4′,5,7-trihydroxyflavanone (0.272 g, 1 mmol) and triethylamine (0.42 ml, 2.9 mmol) in acetonitrile (10 ml) to afford 4′,5,7-trihydroxy-6-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-ylliron(0)}flavanone (**8**) (0.154 g, 3%), 4′,5,7-trihydroxy-8-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**10**) (0.038 g, 0.7%) and 4′,5,7-trihydroxy-6,8-bis-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**12**) (0.029 g, 4%) as a dark viscous golden oil. Similarly tricarbonyl[(1,2,3,4,5 - η) - 2 - methoxycyclohexadienyl]iron(1 +) hexafluorophosphate(1 −) (0.867 g, 2.2 mmol) was reacted with 4′,5,7-trihydroxyflavanone (0.272 g, 1 mmol) and triethylamine (0.42, 2.9 mmol) to afford 4′,5,7-trihydroxy-6,8-bis-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**12**) (0.357 g, 46%).

4′,5,7-Trihydroxy-6-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**8**). IR ($CHCl_3$): ν_{max} 2051, 2042, 1971 (FeCO), 1622 (C=O) cm^{-1}. MS (FAB) *m*/*z* (rel. int. %): 521 (MH^+, 16), 464 ($M^+ - 2CO$, 100), 434 (63), 315 (22), 136 (24). HRMS (FAB) Calc. for $C_{25}H_{21}O_9Fe$ (MH^+), 521.0535. Found: 521.0535. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.99 (m, 1H, 6″α-H), 2.14 (m, 1H, 6″β-H), 2.59 (dd; *J* 5.0, 3.0 Hz; 1H, 4″-H), 2.76 (m, 1H, 3α-H), 3.06 (m, 1H; 3β-H), 3.45 (m, 1H, 1″-H), 3.68 (s, 3H, 2″-OMe), 4.22 (m, 1H, 5″β-H); 5.15 (m, 1H, 2-H); 5.30 (d, *J* 6.0 Hz, 1H, 3″-H), 5.90 (s, 1H, 8-H), 6.80 (d, *J* 8.0 Hz, 2H; 3′,5′-H), 7.34 (d, *J* 8.0 Hz, 2H; 2′,6′-H); 12.50 (s, 1H, 5-OH).

4′,5,7-Trihydroxy-8-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**10**). IR ($CHCl_3$): ν_{max} 2050, 2041, 1970 (FeCO), 1620 (C=O) cm^{-1}. MS (FAB) *m*/*z* (rel. int. %): 521 (MH^+, 8), 464 ($M^+ - 2CO$, 34), 448 (16), 435 (26), 391 (41), 149 (100), 136 (49). HRMS (FAB) Calc. for $C_{25}H_{21}O_9Fe$ (MH^+), 521.0535. Found: 521.0535. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.98 (m, 1H, 6″α-H), 2.15 (m, 1H, 6″β-H), 2.58 (dd; *J* 6.0, 3.0 Hz; 1H, 4″-H), 2.77 (dd; *J* 15.0, 4.0 Hz, 1H, 3α-H), 3.06 (dd; *J* 15.0, 6.0 Hz; 1H; 3β-H), 3.45 (m, 1H, 1″-H), 3.68 (s, 3H, 2″-OMe), 3.69 (m, 1H, 5″β-H); 5.11 (m, 1H, 2-H); 5.30 (d, *J* 11.0 Hz, 1H, 3″-H), 5.86 (s, 1H, 6-H), 6.88 (d, *J* 8.0 Hz, 2H; 3′,5′-H), 7.31 (d, *J* 8.0 Hz, 2H; 2′,6′-H); 12.50 (s, 1H, 5-OH).

4′,5,7-Trihydroxy-6,8-bis-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**12**). IR ($CHCl_3$): ν_{max} 2051, 2040, 1971 (FeCO), 1623 (C=O) cm^{-1}. MS (FAB) *m*/*z* (rel. int. %): 769 (MH^+, 35), 712 ($M^+ - 2CO$, 52), 683 (100), 653 (17), 629 (29), 596 (55), 543 (45), 421 (36), 249 (76). HRMS (FAB) Calc. for $C_{35}H_{29}O_{13}Fe_2$ (MH^+), 769.0317. Found: 769.0317. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.98 (m, 2 × 1H, 6″α-H), 2.14 (m, 2 × 1H, 6″β-H), 2.59 (m, 2 × 1H, 4″-H), 2.76 (m, 1H, 3α-H), 3.06 (m, 1H; 3β-H), 3.45 (m, 2 × 1H, 1″-H), 3.68 (s, 2 × 3H, 2″-OMe), 3.69 and 4.22 (2 × m, 2 × 1H, 5″β-H); 5.08 (m, 2 × 1H, 2-H); 5.30 (m, 2 × 1H, 3″-H), 6.85 (d, *J* 8.0 Hz, 2H; 3′,5′-H), 7.32 (d, *J* 8.0 Hz, 2H; 2′,6′-H); 12.50 (s, 1H, 5-OH).

*4.1.5. 3′,5,7-Trihydroxy-4′-methoxy-6-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**13**), 3′,5,7-trihydroxy-4′-methoxy-8-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**15**), and 3′,5,7-trihydroxy-4′-methoxy-6,8-bis-*

*{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]-iron(0)}flavanone (**17**)*

By the general procedure, tricarbonyl[(1,2,3,4,5-η)cyclohexadienyl]iron(1 +) hexafluorophosphate(1 −) (**2**) (0.363 g, 1 mmol) was reacted with 3′,5,7-trihydroxy-4′-methoxyflavanone (0.302 g, 1 mmol) and triethylamine (0.42 ml, 2.9 mmol) in acetonitrile (10 ml) to afford 3′,5,7-trihydroxy-4′-methoxy-6-{tricarbonyl-[(1″,2″,3″,4″-η) - 1″,3″ - cyclohexadien - 5″α - yl]iron(0)}-flavanone (**13**) (0.0603 g, 11%), 3′,5,7-trihydroxy-4′-methoxy-8-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**15**) (0.0247 g, 5%) and 3′,5,7-trihydroxy-4′-methoxy-6,8-bis-{tricarbonyl[(1″,-2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**17**) (0.0341 g, 5%) as a dark viscous golden oil. Similarly tricarbonyl[(1,2,3,4,5-η)cyclohexadienyl]iron(1 +) hexafluorophosphate(1 −) (0.404 g, 1.1 mmol) was reacted with 3′,5,7-trihydroxy-4′-methoxyflavanone (0.151 g, 0.5 mmol) and triethylamine (0.22 ml, 1.5 mmol) in acetonitrile (10 ml) to afford 3′,5,7-trihydroxy-4′-methoxy-6,8-bis-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**17**) (0.105 g, 28%).

3′,5,7-Trihydroxy-4′-methoxy-6-{tricarbonyl[(1″,2″,-3″,4″ - η) - 1″,3″ - cyclohexadien - 5″α - yl]iron(0)}flavanone (**13**). IR ($CHCl_3$): ν_{max} 2051, 2040, 1968 (FeCO); 1634 (C=O) cm^{-1}. MS (FAB) *m/z* (rel. int. %): 521 (MH^+, 60), 464 ($M^+ - 2CO$, 90), 436 ($M^+ - 3CO$, 100), 362 (21), 285 (22). Anal. Calc. for $C_{25}H_{20}O_9Fe$: C, 57.69; H, 3.85. Found: C, 57.8; H, 3.8%. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.80 (m, 1H, 6″α-H), 2.12 (dq; *J* 11.0, 4.0 Hz; 1H, 6″β-H), 2.76 (dd; *J* 17.0, 2.0 Hz; 1H, 3α-H), 3.04 (m, 2 × 1H; 3β,4″-H); 3.21 (m, 1H, 1″-H), 3.90 (s, 3H, 4′-OMe), 3.91 (m, 1H, 5″β-H), 5.00 (m, 1H, 2-H); 5.25 and 5.38 (2 × m, 2 × 1H; 2″,3″-H), 5.72 (s, 1H, 8-H), 6.87 (m, 2 × 1H; 5′,6′-H), 7.01 (s, 1H, 2′-H); 12.48 (s, 1H, 5-OH).

3′,5,7-Trihydroxy-4′-methoxy-8-{tricarbonyl[(1″,2″,-3″,4″ - η) - 1″,3″ - cyclohexadien - 5″α - yl]iron(0)}flavanone (**15**). IR ($CHCl_3$): ν_{max} 2051, 2040, 1968 (FeCO); 1635 (C=O) cm^{-1}. MS (FAB) *m/z* (rel. int. %): 521 (MH^+, 45), 464 ($M^+ - 2CO$, 40), 436 ($M^+ - 3CO$, 100), 290 (15), 232 (15). HRMS (FAB) Calc. for $C_{25}H_{21}O_9Fe$ (MH^+), 521.0535. Found: 521.0535. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.74 (dd; *J* 16.0, 6.0 Hz; 1H, 6″α-H), 2.06 (m, 1H, 6″β-H), 2.76 (dd; *J* 16.0, 9.0 Hz; 1H, 3α-H); 2.94–3.20 (m, 3 × 1H; 1″,3β,4″-H); 3.90 (m, 1H, 5″β-H), 3.96 (s, 3H, 4′-OMe), 4.98 (m, 1H, 2-H); 5.13 and 5.32 (2 × m, 2 × 1H; 2″,3″-H), 5.70 (s, 1H, 6-H), 6.95 (m, 2 × 1H; 5′,6′-H), 7.08 (s, 1H, 2′-H); 12.06 (s, 1H, 5-OH).

3′,5,7-Trihydroxy-4′-methoxy-6,8-bis-{tricarbonyl-[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**17**). IR ($CHCl_3$): ν_{max} 2051, 2039, 1971 (FeCO), 1624 (C=O) cm^{-1}. MS (FAB) *m/z* (rel. int. %): 739 (MH^+, 28), 682 ($M^+ - 2CO$, 51), 654 ($M^+ - 3CO$, 100), 586 (52), 566 (26), 514 (26), 361 (29). HRMS (FAB) Calc. for $C_{34}H_{27}O_{12}Fe_2$ (MH^+), 739.0201. Found: 739.0201. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.80 (m, 2 × 1H, 6″α-H), 2.08 (m, 2 × 1H, 6″β-H), 2.76 (dd; *J* 17.0, 9.0 Hz; 1H, 3α-H); 2.94–3.20 (m, 5 × 1H; 3β- and 1″,4″-H); 3.90 (s, 3H, 4′-OMe); 3.91 and 4.02 (2 × m, 2 × 1H, 5″β-H); 4.90–5.25 (m, 3 × 1H, 2- and 2″-H); 5.32 and 5.38 (2 × m, 2 × 1H, 3″-H), 6.95 (m, 2 × 1H; 5′,6′-H), 7.01 (s, 1H, 2′-H), 12.40 (s, 1H, 5-OH).

*4.1.6. 3′,5,7-Trihydroxy-4′-methoxy-6-{tricarbonyl[(1″,-2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron-(0)}flavanone (**14**), 3′,5,7-trihydroxy-4′-methoxy-8-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**16**) and 3′,5,7-trihydroxy-4′-methoxy-6,8-bis-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**18**)*

By the general procedure, tricarbonyl[(1,2,3,4,5-η)-2-methoxycyclohexadienyl]iron(1 +) hexafluorophosphate(1 −) (**3**) (0.394 g, 1 mmol) was reacted with 3′,5,7-trihydroxy-4′-methoxyflavanone (0.302 g, 1 mmol) and triethylamine (0.42 ml, 2.9 mmol) to afford 3′,5,7-trihydroxy-4′-methoxy-6-{tricarbonyl[(1″,2 ″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**14**) (0.0847 g, 15%), 3′,5,7-trihydroxy-4′-methoxy-8-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**16**) (0.0169 g, 3%) and 3′,5,7-trihydroxy-4′-methoxy-6,8-bis-{tricarbonyl[(1″,-2″,3″,4″ - η) - 2″ - methoxy - 1″,3″ - cyclohexadien - 5″α - yl]-iron(0)}flavanone (**18**) (0.0246 g, 3%) as a dark viscous golden oil. Similarly tricarbonyl[(1,2,3,4,5-η)-2-methoxycyclohexadienyl]iron(1 +) hexafluorophosphate-(1 −) (0.433 g, 1.1 mmol) was reacted with 3′,5,7-trihydroxy-4′-methoxyflavanone (0.151 g, 0.5 mmol) and triethylamine (0.42 ml, 2.9 mmol) in acetonitrile (10 ml) to afford 3′,5,7-trihydroxy-4′-methoxy-6,8-bis-{tricarbonyl[(1″,2″,3″,4″ - η) - 2″ - methoxy - 1″,3″ - cyclohexadien - 5″α - yl]iron(0)}flavanone (**18**) (0.100 g, 25%).

3′,-5,7-Trihydroxy-4′-methoxy-6-{tricarbonyl[(1″,2 ″,-3″,4″ - η) - 2″ - methoxy - 1″,3″ - cyclohexadien - 5″α - yl]iron-(0)}flavanone (**14**). IR ($CHCl_3$): ν_{max} 2050, 2041, 1971 (FeCO), 1641 (C=O) cm^{-1}. MS (FAB) *m/z* (rel. int. %): 551 (MH^+, 31), 494 ($M^+ - 2CO$, 100), 466 ($M^+ - 3CO$, 98), 451 (20), 315 (19), 136 (33). HRMS (FAB) Calc. for $C_{26}H_{23}O_{10}Fe$ (MH^+), 551.0641. Found: 551.0641. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.99 (dm, *J* 12.0 Hz, 1H, 6″α-H), 2.14 (dq; *J* 12.0, 4.0 Hz; 1H, 6″β-H), 2.59 (dd; *J* 6.0, 3.0 Hz; 1H, 4″-H), 2.76 (dd; *J* 17.0, 2.0 Hz; 1H, 3α-H), 3.45 (m, 1H; 3β-H), 3.49 (m, 1H, 1″-H), 3.68 (s, 3H, 2″-OMe), 3.69 (m, 1H, 5″β-H), 3.90 (s, 3H, 4′-OMe), 5.15 (m, 1H, 2-H); 5.27 (m, 1H, 3″-H), 5.70 (s, 1H, 8-H), 6.88 (m, 2 × 1H; 5′,6′-H), 7.02 (s, 1H, 2′-H); 12.49 (s, 1H, 5-OH).

3′,5,7-Trihydroxy-4′-methoxy-8-{tricarbonyl[(1″,2″,-3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron-(0)}flavanone (**16**). IR ($CHCl_3$): ν_{max} 2050, 2042, 1970 (FeCO), 1640 (C=O) cm^{-1}. MS (FAB) *m/z* (rel. int. %): 551 (MH^+, 50), 494 ($M^+ - 2CO$, 65), 466 ($M^+ - 3CO$, 100), 315 (25), 249 (11), 136 (20). HRMS (FAB) Calc. for $C_{26}H_{23}O_{10}Fe$ (MH^+), 551.0641. Found: 551.0641. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.90 (m, 1H, 6″α-H), 2.09 (dq; *J* 13.0, 5.0 Hz; 1H, 6″β-H), 2.56 (m, 1H, 4″-H), 2.77 (m, 1H, 3α-H), 3.02 (m, 1H; 3β-H), 3.25 (m, 1H, 1″-H), 3.35 (m, 1H, 5″β-H), 3.41 (s, 3H, 2″-OMe), 3.94 (s, 3H, 4′-OMe), 4.99 (m, 1H, 2-H); 5.28 (m, 1H, 3″-H), 5.73 (s, 1H, 6-H), 6.91 (m, 2 × 1H; 5′,6′-H), 7.02 (s, 1H, 2′-H); 12.79 (s, 1H, 5-OH).

3′,5,7-Trihydroxy-4′-methoxy-6,8-bis-{tricarbonyl-[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]-iron(0)}flavanone (**18**). IR ($CHCl_3$): ν_{max} 2050, 2041, 1968 (FeCO), 1635 (C=O) cm^{-1}. MS (FAB) *m/z* (rel. int. %): 799 (MH^+, 12), 742 ($M^+ - 2CO$, 68), 714 ($M^+ - 3CO$, 100), 683 (20), 646 (45), 626 (70), 598 (46), 421 (42), 361 (61). HRMS (FAB) Calc. for $C_{36}H_{31}O_{14}Fe_2$ (MH^+), 799.0400. Found: 799.0400. NMR, ^1H: δ (400 MHz, $CDCl_3$) 1.76 (m, 2 × 1H, 6″α-H), 2.13 (m, 2 × 1H, 6″β-H), 2.57 (m, 2 × 1H, 4″-H), 2.75 (m, 1H, 3α-H), 2.99 (m, 1H; 3β-H); 3.26 and 3.40 (2 × m, 2 × 1H, 1″-H); 3.47 and 3.70 (2 × m, 2 × 1H, 5″β-H); 3.48 and 3.71 (2 × s, 2 × 3H, 2″-OMe); 3.91 (s, 3H, 4′-OMe), 5.12 (m, 1H, 2-H), 5.24 (m, 2 × 1H, 3″-H), 6.90 (m, 2 × 1H; 5′,6′-H), 7.00 (s, 1H, 2′-H); 12.62 (s, 1H, 5-OH).

4.1.7. Preparation of 4′,5,7-trihydroxy-6-{tricarbonyl-[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}-flavanone (7) using NaH for deprotonation

To a stirred solution of 4′,5,7-trihydroxyflavanone (0.272 g, 1.0 mmol) in THF (40 ml) was added NaH (0. 145 mg, 6 mmol) at −78°C. The resulting solution was stirred for 1 h at −78°C. Tricarbonyl[(1,2,3,4,5-η)cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**2**) (0.364 g, 1 mmol) was added in one portion and the mixture was stirred for a further 15 min at −78°C. The reaction mixture was allowed to warm to r.t. and left to stir overnight. Water (50 ml) was added and the mixture was extracted with diethyl ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Further purification was performed as described in the general procedure to afford 4′,5,7-trihydroxy-6-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (**7**) (0.43 g, 88%).

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