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Flavonoid derivatives as organometallic bioprobes☆

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Abstract

The synthesis of organoiron derivatives of biologically active flavonoids is described. Lithium enolates of functionalised protected acetophenones and metallated derivatives of substituted aromatic rings have been employed as nucleophiles in combination with tricarbonyl(η^5-cyclohexadienyl)iron electrophiles. Products have been converted into flavonoid and chalcone derivatives. Enolates generated from protected flavanones have also been used in nucleophile addition reactions, and a one-pot in situ protection, nucleophile addition, deprotection sequence is reported.

Keywords: Flavonoids; Root nodulation; *Rhizobium*; Gene induction; Signal molecules; Organometalcarbonyl groups; Tricarbonyliron; Synthesis; Bioprobes

1. Introduction

Bioprobes are functional molecules or devices that provide information about biological systems. They can operate on a macroscopic, microscopic, or submicroscopic scale (bionanometrology and molecular scale observation of biological systems). Our recent work in Nottingham and Norwich has been developing procedures for such sensing molecules based on novel analysis of spectroscopic responses from organometalcarbonyl groups [1–11]. Organometal structures are rare in nature, so there is no cross-talk with background signals, and organometalcarbonyl groups have intense IR vibrational bands that can be observed in a window in the water background spectrum [12]. These bands are narrow, so several can be observed in a single experiment [2,11,13], and respond to changes in solvation environment [1], providing the basis for our molecular scale sensors and bioprobes. Over the past few years, we have established many of the essential features needed for such applications. Principal component analysis of FTIR spectra has been used to differentiate responses to different solvents [1] and mixtures of solvents [1,2], different ions associated with crown ethers [3], and changes in pH [4]. The method can detect π-stacking [5] and ionic recognition [6] in the host–guest chemistry of charged heteroaromatic compounds, and differentiate between barbituate structures by subtle changes in hydrogen bonding to host–guest receptors [7]. The organometalcarbonyl groups have been attached to proteins [8] to allow ionisation changes on protein surface groups to be studied [9]. Supported organometallics have been used in combination with ATR elements [10] and fibre optics [11] to facilitate sampling. The methods established in this way should be suitable for use with FTIR microscopy [14] and FTIR imaging [15] technologies. Improvements in methodologies for

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synthetic chemistry are now needed to prepare more advanced and optimised organometalcarbonyl derivatives for use in combination with our FTIR procedures, and this is becoming a major focus for the development of new organometallic bioprobes. Our first explorations in this direction with bioflavonoids have been the subject of a preliminary communication [16]. The synthesis of bioflavonoids bearing organometallic groups should provide a series of valuable spectroscopic probes. Since the pioneering preparation [17] of organometallic derivatives of estradiols by the Jaouen group, and the demonstration of their retained biological activity [18], it has become clear that the introduction of additional organometal-bearing substituents does not preclude retained binding ability with the natural biological receptors. Since then, prospects for novel applications of organometallic chemistry in biology have been reviewed by Ryabov [19] and Beck [20], significant advances have been made through developments in the CMIA technique [21], and a variety of organometalcarbonyl-tagged natural products have been prepared for spectroscopic investigation [17,22–26]. This growing focus on the prospects for novel applications of organometallic systems in biology has recently culminated in the first International Symposium on Bio-organometallic Chemistry (ISBOMC'02) which marks the beginning of a wider interest in these procedures that will take this area of chemistry beyond the domain of specialised research groups into the wider chemical, biological chemistry, and biochemical communities.

In our present work, we have been addressing the synthesis of organometalcarbonyl derivatives of a series of A/B-ring oxygenated flavonoids that are active in the control of root nodulation [27], a prerequisite for nitrogen fixation in plants. Induction of nodulation (*nod*) gene expression in symbiotic *Rhizobium* bacteria is a crucial event in the early stages of legume root nodulation, and plant-derived flavonoid signal molecules such as naringenin (**1**) and eriodictyol (**2**) effect the gene induction process. These biological processes are summarised in Fig. 1. It has been shown that OH groups must be present on both A and B-rings for efficient biological activity. In recent years, the molecular signalling that controls root nodulation (Fig. 1a) has been the subject of sustained research effort, culminating in the identification [28] and total synthesis [29] of NodRm-IV factors (sulfated lipooligosaccharides), the *Rhizobium* nodulation signal molecules that are released by the bacteria as a response to the presence of flavonoid *nod* gene inducing compounds originating from legumes. For some time, it has also been known from experiments with mutant Rhizobium strains that the constitutive *nodD* gene is essential for *nod* gene induction (Fig. 1b) that leads to the production of the NodRm-IV factors [30], giving rise to the proposal that recognition of plant-derived flavonoids by binding to the gene-product NodD initiates the production of the bacterial nodulation signal molecules, which, in turn, effect changes in legume root cells that lead to root-hair deformation [31] and the onset of root nodulation by infestation by *Rhizobium*. The objective of our work has been to prepare organometallic flavonoid derivatives which retain their capacity to induce *nod* gene expression, in preparation for their use in an FTIR investigation of the organometalcarbonyl probe in the presence of protein-containing fractions of lysed cells from $nodD^+$ and $nodD^-$ strains of

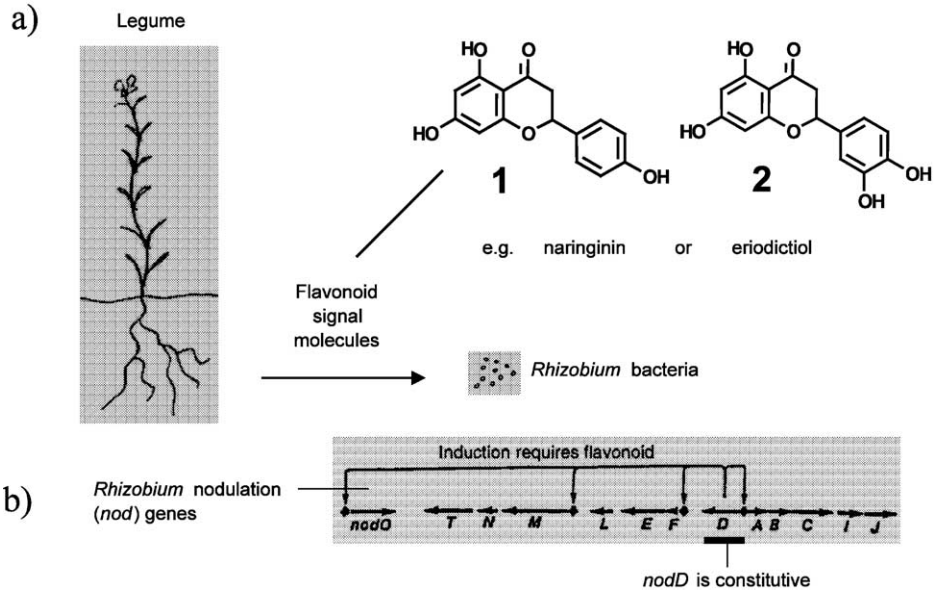


Fig. 1. Cartoon to illustrate signalling (a) and *nod* gene induction events (b) at the first stage of root nodulation in legumes.

Rhizobium. The practicality of FTIR observation of this class of compounds at biologically relevant concentrations (50 μM) has been established [16] in the presence of lysed cells of *Rhizobium leguminosarum* (8400pRL1) carrying *nodD* on pIJ1518, and an isogenic strain lacking *nodD*. The prime objective now is the search for flavonoid derivatives with substantial residual biological activity, so that differences between the IR spectra in the carbonylmetal vibrational region (2040–1900 cm^{-1}) can be used to prove that the flavonoid binds to the NodD protein, and reveal details of the nature of the putative binding site. Our approach is to prepare a representative set of flavonoids (Fig. 2) with the organometallic moiety attached at the A-, B- or C-rings, and to compare their activity in a screen for *nod* gene induction.

The introduction of the A-ring substituent proved straight-forward by direct reaction between the flavanone and a tricarbonyl(η^5-cyclohexadienyl)iron complex, and full details of these procedures have already been reported [32] (direct introduction of electrophilic carbonylcobalt alkyne complexes to natural products with oxygenated aromatic rings has also been reported [25]). We now describe details of progress towards the more challenging synthetic routes needed for the B and C-ring derivatives that will complete the set of structures required (Fig. 2) for the initial biological evaluation.

2. Results and discussion

2.1. Synthetic strategies for B-ring substitution

Since the electrophilic substitution of oxygenated flavanones occurs readily at ring A, intact flavanones were the logical starting point for the preparation of A-ring substituted derivatives (Fig. 3a), and commercially-available compounds were convenient for this purpose [32]. It follows, however, that if the organometallic substituent is required on the B-ring, it should be attached to the aromatic ring before the formation of the flavanone (Fig. 3b). A number of metallation strategies could be chosen for this purpose, and at the start of our investigations towards the B-ring series, we compared several metallated derivatives to establish their suitability in combination with tricarbonyl(η^5-cyclohexadienyl)iron electrophiles. Metallation next to OMe groups is well known [33], and since the required building block is a benzaldehyde derivative, an acetal-protected benzaldehyde with an ether substituent was evaluated first, but without success (Table 1: entries 1–3). Metallation of the ethanediol acetal of 4-methoxybenzaldehyde with *n*-butyllithium, followed by attempted reaction of the resulting aryllithium reagent with the tricarbonyliron complex **4** was the starting point for this work, but no products corresponding to

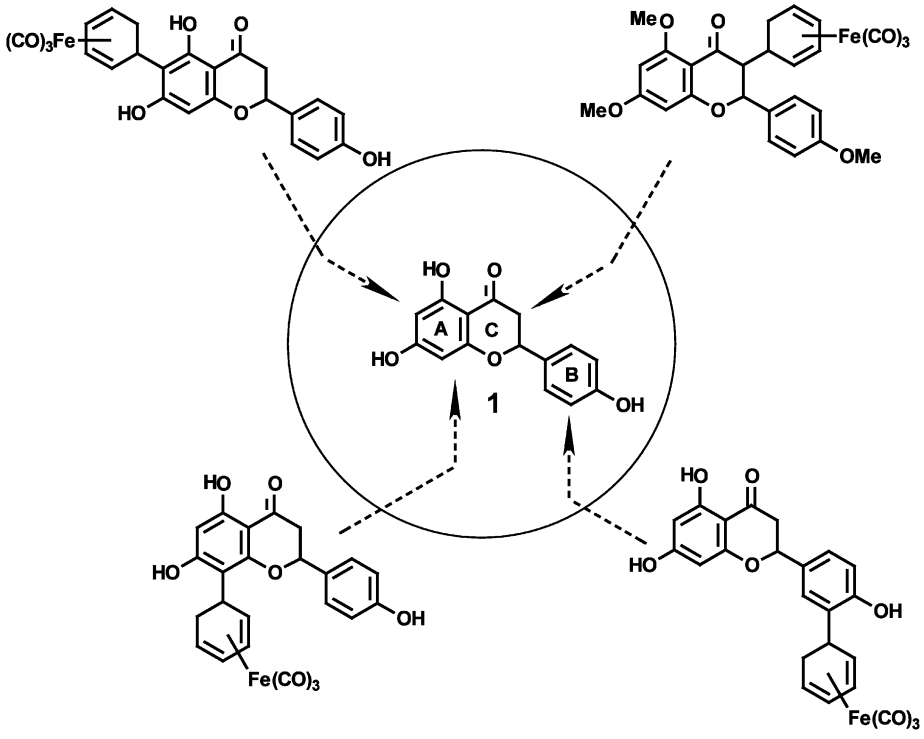


Fig. 2. Labelling strategies to explore the point of attachment of tricarbonyl(η^5-cyclohexadienyl) iron groups around the periphery of bioactive flavanoids.

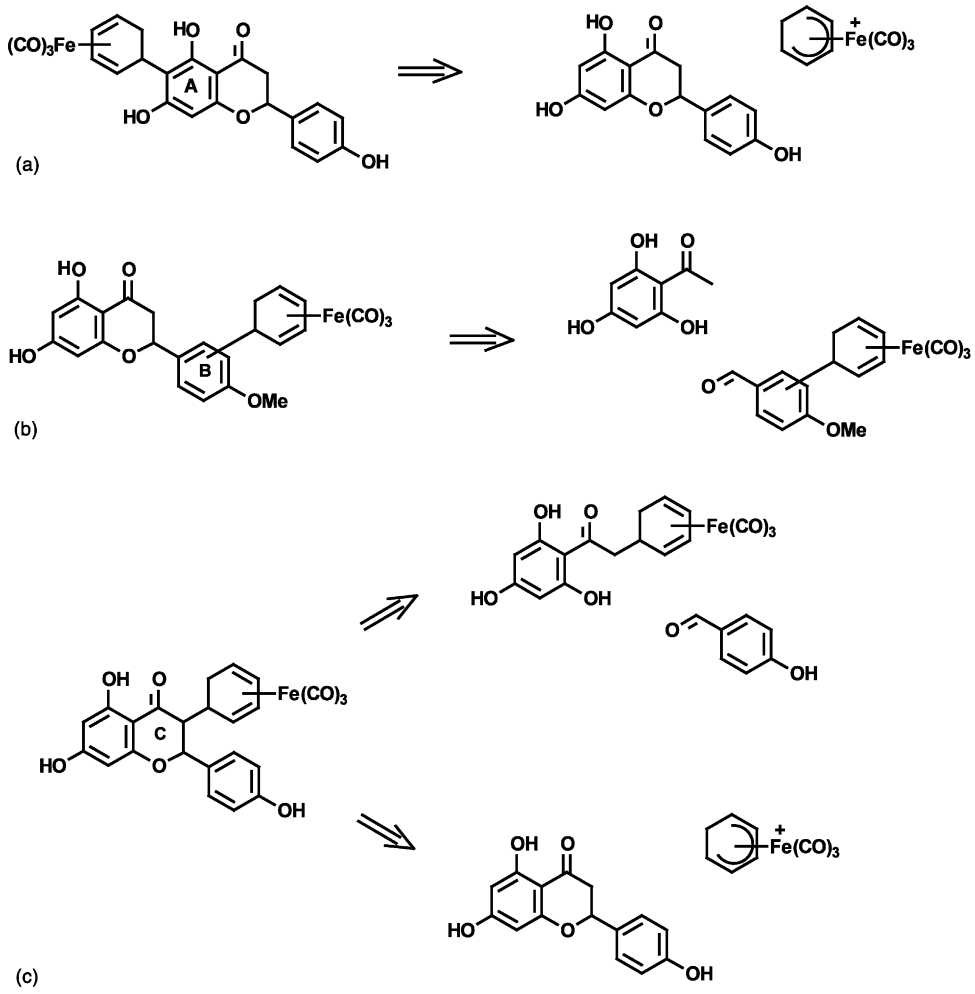


Fig. 3. Disconnections to illustrate reterosynthetic strategies for the A (a), B (b) and C (c) ring substitution patterns.

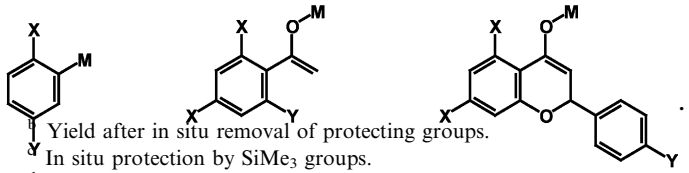
nucleophile addition to the dienyl salt were obtained. In a protracted series of experiments, variation of the phenol protecting group (methyl, *t*-butyldimethylsilyl, allyl) the metallating agent (*n*-butyllithium, *s*-butyllithium, *t*-butyllithium and *n*-butyllithium/potassium *tert*-butoxide) and solvent (ether, tetrahydrofuran (THF), dichloromethane, and hexane in the case of the Schlosser base) were all examined. Attention turned next (Scheme 1) to the oxazoline derivative **3** which was prepared from 4-methoxybenzoyl chloride by the literature procedure [34]. This approach proved far more successful. Metallation of **3** with *s*-butyllithium in ether [35], and addition of the electrophile **4** to the resulting aryllithium reagent, now afforded the expected adduct **5** in 76% yield (Table 1: entry 4). When this reaction was repeated with the less reactive electrophile **7**, the corresponding adduct **8** was again obtained, but in a reduced yield (Table 1: entry 5). Conversion of the oxazoline into the aldehyde is possible by quaternisation and hydride reduction. This reaction was attempted first with the metal complex **5**. Reaction with methyl iodide, followed by reduction with L-selectride and acid-catalysed hydrolysis of the heterocyclic ring, afforded the required benzaldehyde derivative **6**, but in only 20% yield, and then as a 1:1 mixture with recovered starting material. Product **6** was tentatively identified from an NMR spectrum of the mixture of products. The reaction was repeated with the adduct **8**, but none of the corresponding benzaldehyde adduct was obtained. In view of these problems, further attempts at optimisation of the production of **6** and further characterisation of this compound was not attempted.

A new approach was based on lithium-for-halogen exchange which provided an alternative procedure for the generation of the aryllithium reagents, and two B-ring substitution patterns were addressed (Schemes 2 and 3) starting from either 3-bromophenol by formylation, protection and metallation, or from 4-hydroyxbenzaldehyde by bromination, protection, and metallation. Formylation of 3-bromophenol (Scheme 2) using the Reimer–Tiemann conditions as described by Hodgson [36] gave the known 2-bromo-4-hydroxybenzaldehyde which was purified by column chromatography. Silylation with *t*-butyldimethylsilyl chloride

Table 1
Nucleophile addition reactions with tricarbonyl(η^5-cyclohexadienyl)iron(1+) electrophiles

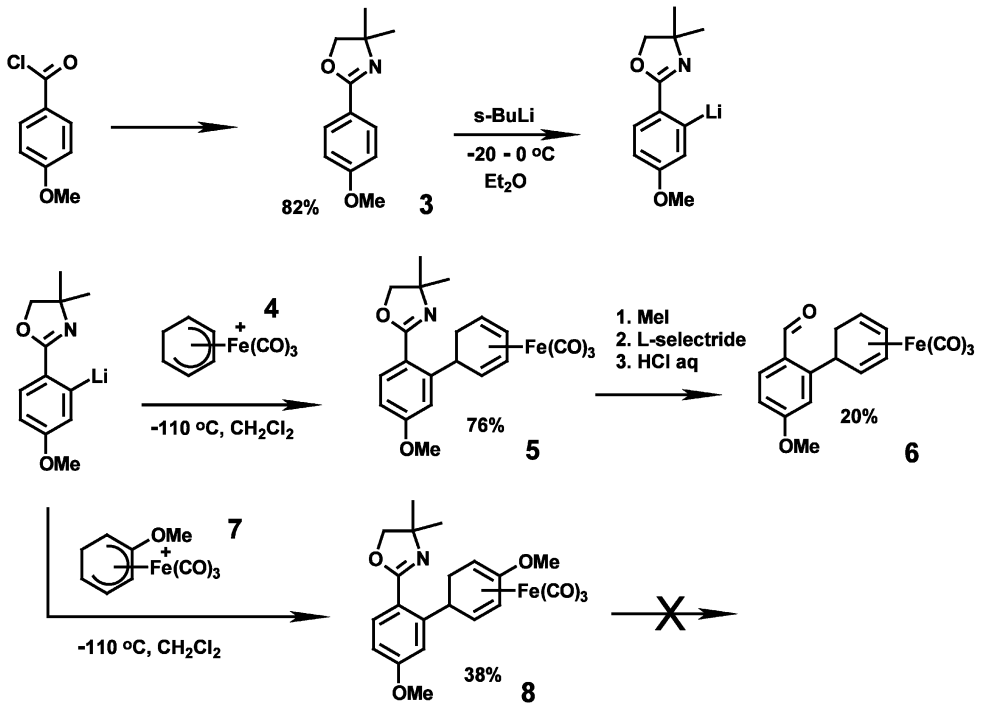
Entry	Nucleophile [a]			Metal	Electrophile		Product		
		Type	Derived from: [Structure]			R		%	Type
1	–	Metallated arene	Arene [**41**: X = OMe, Y = CH(–O–CH_2–CH_2O–)]	M = Li	**4**	H	–	0	–
2	–	Metallated arene	Arene [**41**: X = $OSiMe_2t$-Bu, Y = CH(–O–CH_2–CH_2O–)]	M = Li	**4**	H	–	0	–
3	–	Metallated arene	Arene [**41**: X = $OCH_2CH{=}CH_2$, Y = CH(–O–CH_2–CH_2O–)]	M = Li	**4**	H	–	0	–
4	**3**	Metallated arene	Arene [**41**: X = C(=N–CMe_2–CH_2O–), Y = OMe]	M = Li	**4**	H	**5**	76	Arene derivative
5	**3**	Metallated arene	Arene [**41**: X = C(=N–CMe_2–CH_2O–), Y = OMe]	M = Li	**7**	OMe	**8**	38	Arene derivative
6	**9**	Metallated arene	Bromoarene [**41**: X = CH(–O–CH_2–CH_2O–), Y = $OSiMe_2t$-Bu]	M = Li	**4**	H	**10**	7 [b]	Arene derivative
7	–	Metallated arene	Bromoarene [**41**: X = OMe, Y = CH(–O–CH_2–CH_2O–)]	M = Li	**4**	H	**11**	9 [b]	Arene derivative
8	–	Metallated arene	Bromoarene [**41**: X = OMe, Y = CH(–O–CH_2–CH_2O–)]	M = Li	**7**	OMe	**12**	15 [b]	Arene derivative
9	–	Metallated arene	Aryllithium reagent from bromoarene [**41**: X = OMe, Y = CH(–O–CH_2–CH_2O–)]	M = (CuLi)/2	**4**	H	**11**	57 [b]	Arene derivative
10	–	Metallated arene	Aryllithium reagent from bromoarene [**41**: X = OMe, Y = CH(–O–CH_2–CH_2O–)]	M = (CuLi)/2	**7**	OMe	**12**	67 [b]	Arene derivative
11	**17**	Silylenol ether	Enolate from acetophenone derivative [**42**: X = Y = H]	M = $SiMe_3$	**7**	OMe	**18**	60	Acetophenone derivative
12	**21**	Silylenol ether	Enolate from acetophenone derivative [**42**: X = Y = OMe]	M = $SiMe_3$	**7**	OMe	**22**	72	Acetophenone derivative
13	**26**	Silylenol ether	Enolate from acetophenone derivative [**42**: X = Y = $OSiMe_3$]	M = $SiMe_3$	**7**	OMe	–	0	–
14	**31**	Silylenol ether	Enolate from flavanone derivative [**43**: X = Y = $OSiMe_3$]	M = $SiMe_3$	**4**	H	–	0	–
15	**23**	Lithium enolate	Acetophenone derivative [**42**: X = Y = OMe]	M = Li	**4**	H	**30**	53 [b]	Acetophenone derivative
16	**28**	Lithium enolate	Acetophenone derivative [**42**: X = CH_2OMe, Y = $OSiMe_3$] [c]	M = Li	**7**	OMe	**24**	73	Acetophenone derivative
17	**32**	Lithium enolate	Flavanone derivative [**43**: X = Y = $OSiMe_3$]	M = Li	**4**	H	–	0	–
18	**35**	Lithium enolate	Flavanone derivative [**43**: X = Y = OMe]	M = Li	**4**	H	**36, 37**	64, 23	Flavanone and chalcone
19	–	Lithium enolate	Flavanone derivative [**43**: X = Y = OH] [c]	M = Li	**7**	OMe	**40**	8 [b]	Flavanone
20	–	Lithium enolate	Flavanone derivative [**43**: X = Y = OH] [c]	M = Li	**4**	H	**39**	20 [b]	Flavanone
21	–	Lithium enolate	Flavanone derivative [**43**: X = Y = OH] [d]	M = Li	**7**	OMe	**40**	31 [b]	Flavanone
22	**19**	Copper-mod. enolate	Enolate from acetophenone derivative [**42**: X = Y = OH]	M = (CuLi)/2	**4**	H	**20**	90	Acetophenone derivative
23	**25**	Copper-mod. enolate	Enolate from acetophenone derivative [**42**: X = Y = OMe]	M = (CuLi)/2	**4**	H	**24**	72	Acetophenone derivative
24	**27**	Copper-mod. enolate	Flavanone derivative [**42**: X = Y = $OSiMe_3$]	M = (CuLi)/2	**4**	H	**–**	0	–
25	**33**	Copper-mod. enolate	Flavanone derivative [**43**: X = Y = $OSiMe_3$]	M = (CuLi)/2	**4**	H	–	0	–
26		Copper-mod. enolate	Flavanone derivative [**43**: X = Y = OMe]	M = (CuLi)/2	**7**	OMe	**38**	28	Chalcone
27		Sodium enolate	Flavanone derivative [**43**: X = Y = OMe]	M = Na	**7**	OMe	**38**	23	Chalcone

[a] Generalised structures of nucleophiles:



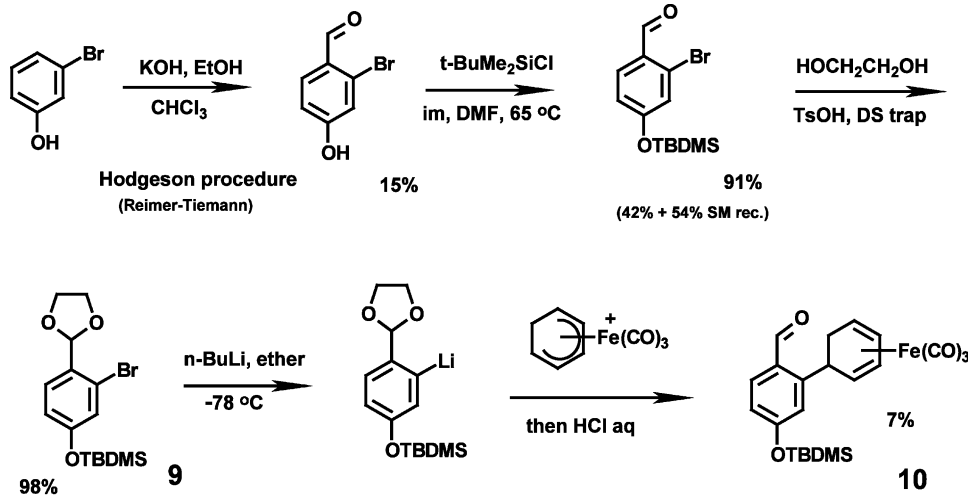
41 **42** **43**

[b] Yield after in situ removal of protecting groups.
[c] In situ protection by $SiMe_3$ groups.
[d] In situ protection by CH_2OMe groups.

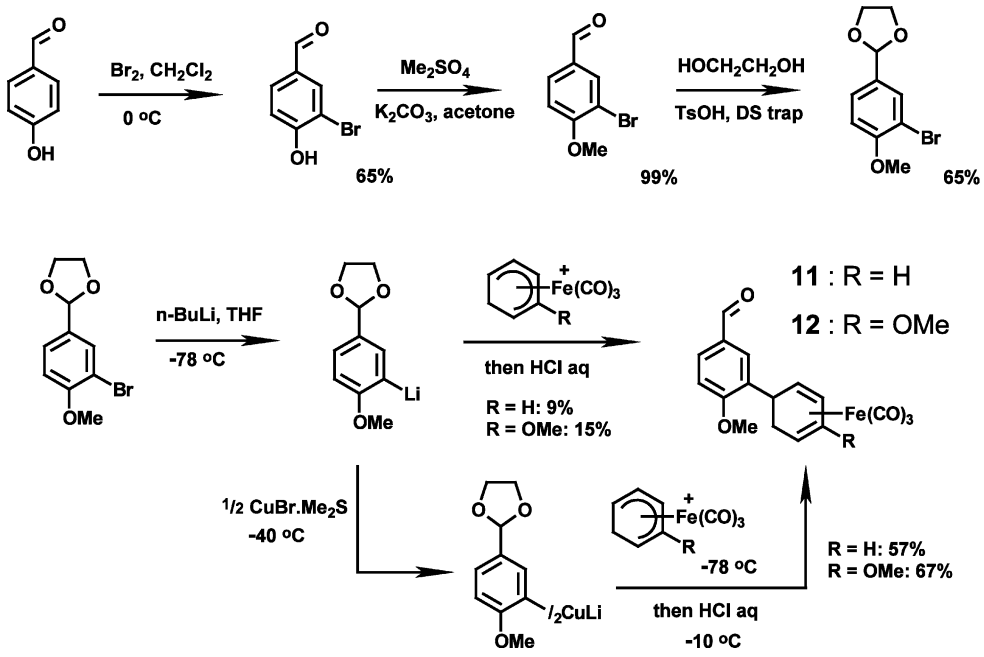


Scheme 1.

introduced a bulky protecting group at the phenolic oxygen, chosen to minimise possible complications through migration [37] of the site of metallation of the aromatic ring. Conversion into the acetal, as before, afforded the protected bromoarene **9**. Lithium-for-bromine exchange with *n*-butyllithium followed by addition of the cyclohexadienyliron complex **4** and hydrolysis of the product in aqueous acid, led directly to the formation of the adduct **10** of the silyloxybenzaldehyde, but in only 7% yield (Table 1: entry 6). The efficiency of addition of aryllithium reagents to tricarbonyl(η^5-cyclohexadienyl)iron complexes is clearly very sensitive to the nature of substituents on the aromatic ring, and in the case of **9** the combination of acetal and TBDMS ether is far less desirable than the oxazoline/methyl ether pairing in **3**. Fortunately, the alternative of bromination of 4-hydroxybenzaldehyde proved more successful (Scheme 3). A small ether protecting group was chosen, and after acetalisation, lithium-for-bromine exchange with *n*-butyllithium afforded the aryllithium reagent which was employed as a nucleophile with salts **4** and **7** using an acidic work-up, as before, to give direct access to the derivatised benzaldehydes. The products **11** and **12** were obtained in this way in slightly improved yields in the range 9–15% (Table 1: entries 7, 8). Further improvement was

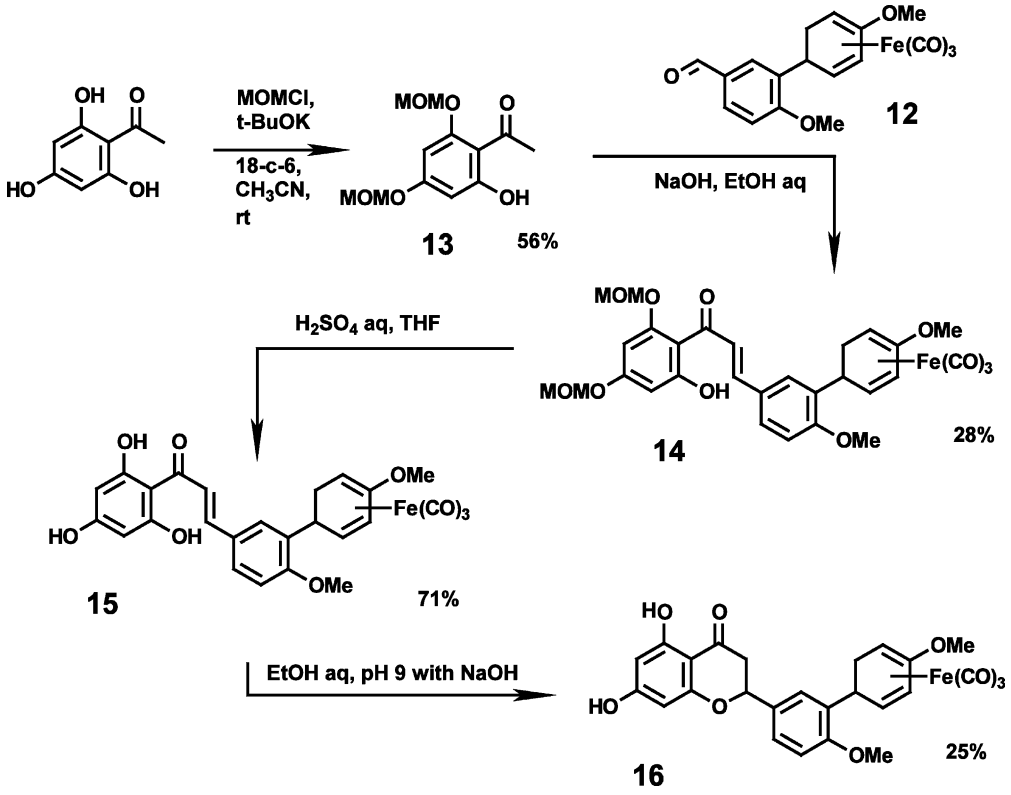


Scheme 2.



Scheme 3.

obtained by conversion of the aryllithium reagent into an organocuprate [37,38]. In this way, yields of **11** and **12** were raised to 57 and 67%, respectively, (Table 1: entries 9, 10). The adduct **12** was taken on to the flavanone (Scheme 4). Condensation of **12** with the partially protected [39] trihydroxyacetophenone **13** afforded **14**. Removal of the MOM protecting groups with acid, afforded the chalcone derivative **15** in 20% yield. Since flavanone and chalcone species are likely to interconvert under biological conditions, this product might itself be suitable for biological evaluation, and was fully characterised. Although well precedented [40],



Scheme 4.

cyclisation of orthohydroxychalcones to flavanones can be a difficult procedure, but none-the-less, **15** was successfully taken through to provide enough of the flavanone **16** for it to be used in the biological assay for *nod* gene induction. Product **16** was identified by NMR, IR and FAB mass spectrometry, but the high-mass ions in the FAB spectrum, in this case, were of too low an intensity to permit accurate mass confirmation of the structure. Since it is formed by the known cyclisation reaction of the characterised chalcone precursor **15**, high field NMR and low resolution FAB characterisation is sufficient to allow the unambiguous assignment of structure **16** to the product of the cyclisation step.

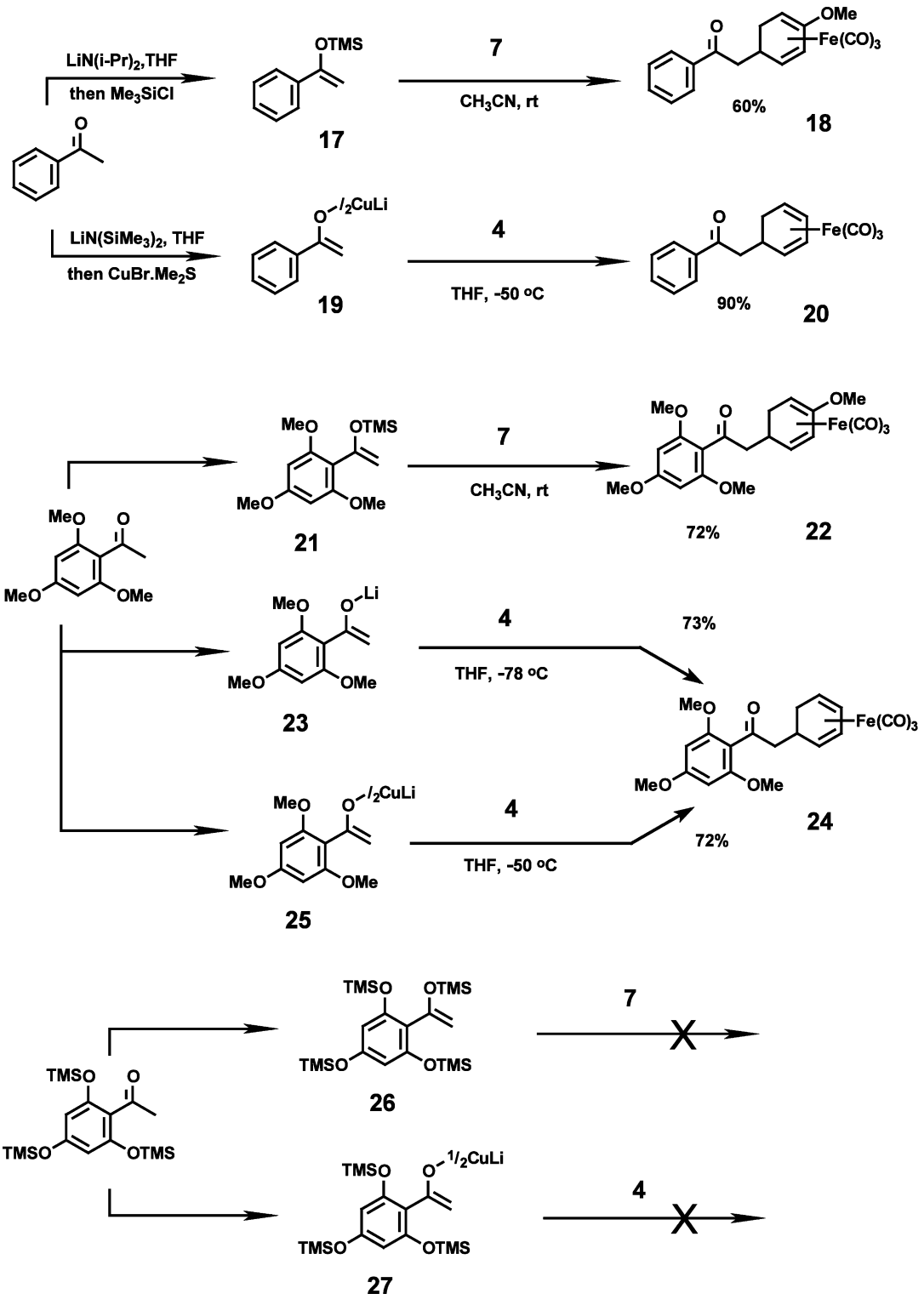
2.2. Synthetic strategies for C-ring substitution

A similar approach (Fig. 3c) can yield a C-ring derivative by introduction of the tricarbonyliron complex prior to formation of the flavonoid, but in principle, direct functionalisation of the intact flavonoid could also provide the required structure. The problem with this direct alternative, however, is that both protection of the flavonoid OH groups, and development of the C-ring enolate, requires great care in order to avoid the opening of the labile central ring. The use of silylenol ethers as nucleophiles with cyclohexadienyliron complexes, on the other hand, is well established [41], and in preliminary model studies (Scheme 5), we tested enol ethers **17** and copper-modified enolates **19** with the cyclohexadienyliron electrophiles **7** and **4** to form **18** and **20** (Table 1: entries 11, 22). The copper-modified enolate gave particularly good results. Similarly, trimethoxyacetophenone derivatives were successfully converted into the corresponding organoiron products **22** and **24**, using either electrophile **4**, or the methoxy-substituted counterpart **7** (Table 1: entries 12, 16, 23). Trimethylsilylenol ethers **21**, lithium enolates **23** and copper-modified enolates **25** were all found to be suitable for the purpose, and the products **22** and **24** were isolated in better than 70% yield in each case. Again, however, these reactions were found to be sensitive to the exact substitution pattern on the nucleophilic reagent, and the corresponding *tetra*- and *tris*-trimethylsilyl nucleophiles **26** and **27** gave no isolable products from reactions with **7** and **4** (Table 1: entries 13, 24). Selective bis protection of 2,4,6-trihydroxyacetophenone is possible (Scheme 4), and the bis-MOM product **13** [39] was further protected with a trimethylsilyl group and converted without isolation into the lithium enolate **28** (Scheme 6). Addition of the cyclohexadienyliron electrophile **7** to form **29**, and a hydrolytic work-up, afforded the required trihydroxyacetophenone derivative **30** (Table 1: entry 15), which should be suitable for the completion of the stepwise route (Fig. 3c) to C-ring adducts, using the same procedures shown in Scheme 4. In fact, for the purpose of initial biological evaluation which is the goal of our current studies, this final step proved unnecessary, as the required adducts were successfully obtained in sufficient quantities for screening by the alternative direct reaction of the flavonoids with electrophilic cyclohexadienyliron complexes, but the preparation of **30** by the stepwise sequence shown in Scheme 6 is important because it provides the key intermediate needed for a higher yielding strategy to gain access to specific C-ring products in future work.

The investigation of the intact flavonoid series began (Scheme 7) with the examination of the *tetra*(trimethylsilyl)naringenin derivative **31**. By means of low temperature conditions, this was successfully prepared in 79% yield, but unlike **18** and **20**, reaction with the tricarbonyl(η^5-cyclohexadienyl)iron complex **4** proved unsuccessful (Table 1: entry 14). The use of the lithium enolate **32** of the *tris*(trimethysilyloxy)flavanone derivative (Table 1: entry 17), and a copper-modified reagent **33** obtained from the unprotected flavanone using LDA and $CuBr \cdot Me_2S$ (Table 1: entry 25) were similarly unsuccessful. The 4′,5,7-trimethoxy derivative **34** [42] was also prepared (Scheme 8) using dimethyl sulfate and potassium carbonate in acetone. This was converted into the lithium enolate **35** and reaction with **4** gave the flavanone adduct **36** in 64% yield, together with the chalcone **37** (Table 1: entry 18). The opening of the central ring could not be completely prevented in this case. Finally (Scheme 9), a practical though relatively low yielding one-pot procedure was developed, in which protection of the phenolic OH groups, deprotonation to generate the enolate, reaction with the tricarbonyliron complex, and deprotection were all performed in single sequence (Table 1: entries 19–21), affording the flavanone derivatives **39** and **40** directly in the form needed for biological evaluation. In situ protection with trimethylsilyl chloride and MOM chloride was compared, and the latter was found to give the better results. The product **40** was obtained in 31% overall yield for the four steps.

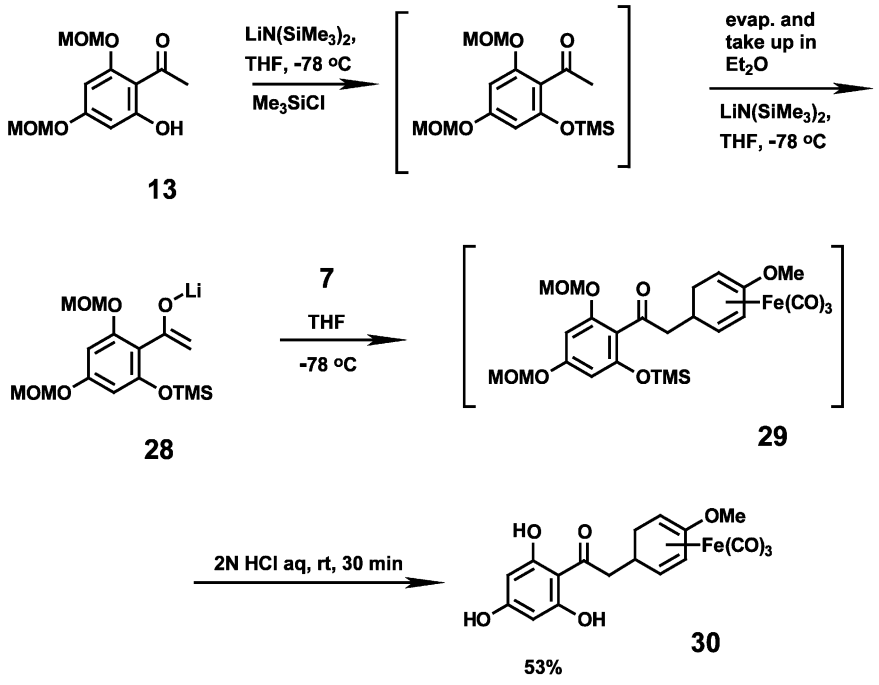
3. Conclusions

The the A-ring products from our previous paper [32], and **16**, **39**, and **40**, described here, are the first tricarbonyliron derivatives of flavanones to be prepared [43]. Commercially-available hydroxyflavanones can be converted into organometallic derivatives by convenient, direct, one-pot procedures (using 3 equivalents of sodium hydride to generate the triphenolate for the A-ring substitution [32], and the in situ protection, enolate generation and deprotection described above for ring C) to afford sufficient material for biological evaluation in screens for nodulation gene induction. Where the flavonoid must be prepared from hydroxyarene components, the alternative of formation of the organometallic



Scheme 5.

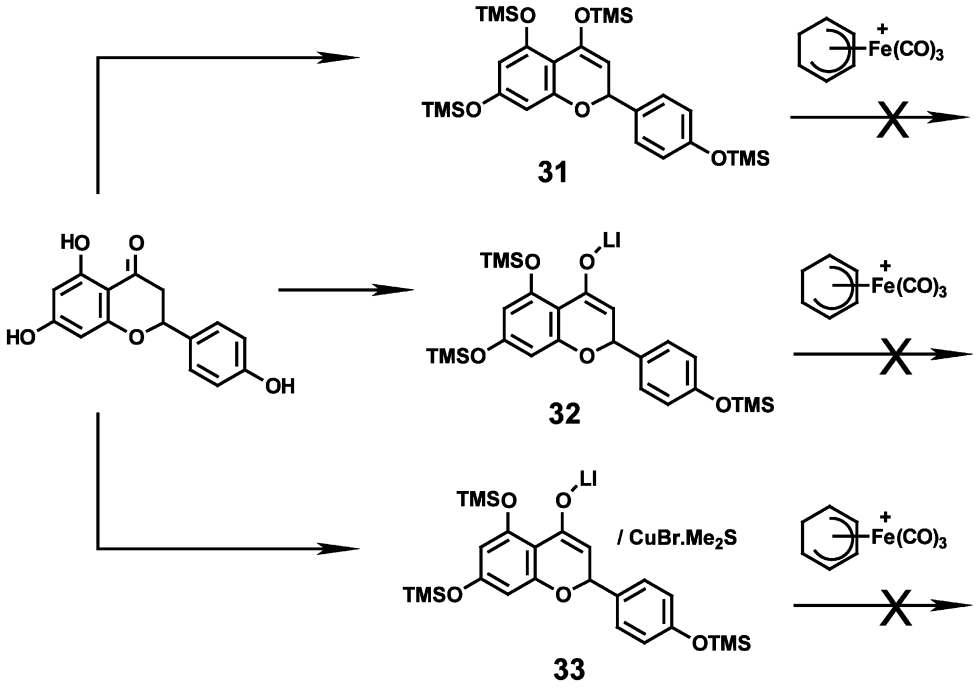
adduct prior to introduction of the B-, C-ring system looks promising, and has successfully yielded the B-ring adduct **16**. Biological testing reported elsewhere [16] has shown that significant residual biological activity is retained in the some of the organometallic products at 20 μM concentrations. Despite the bulk of the additional metal-bearing ring, the metal-tagged product must still be capable of participating in the binding events that underpin the mechanism of the gene induction process. The B- and C-ring adducts described in this



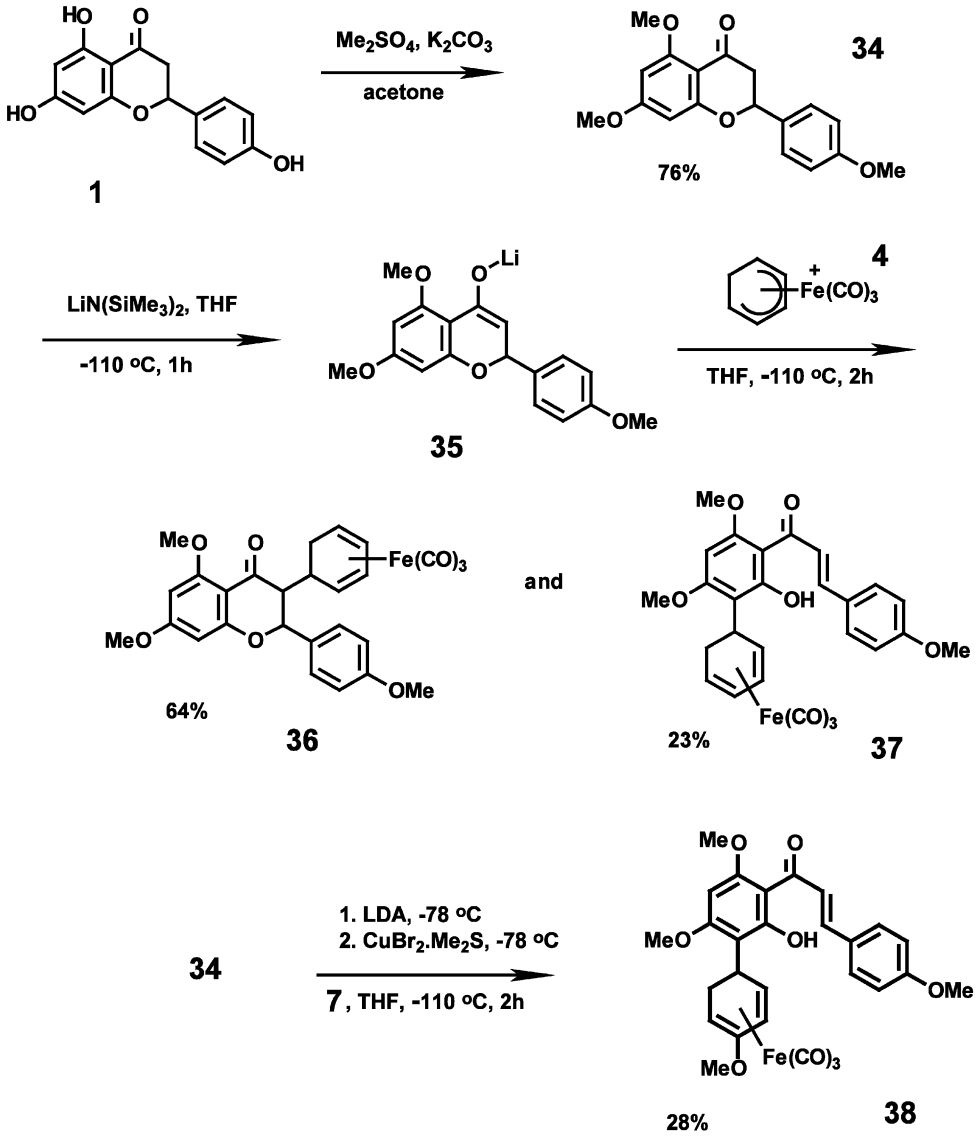
Scheme 6.

paper are an improvement on the A-ring series reported earlier [16,32], as they also show significant *nod* gene induction activity [16] at 2 μM levels (e.g. compound **40**).

In the development of synthetic strategies for these B- and C-ring derivatives, a wide selection of examples of nucleophilic addition to tricarbonyl(η^5-cyclohexadienyl)iron electrophiles have been examined (Table 1), and in contrast to results typical of simple systems [44], the use of highly functionalised intermediates needed for the construction of oxygenated flavonoids has shown that the efficiency of nucleophile addition can be profoundly influenced by the precise nature of substituents, and the choice of protecting group strategies. In this work, we have identified simple procedures (lithium counterions in dichloromethane) for the use of enolates of aceto-



Scheme 7.

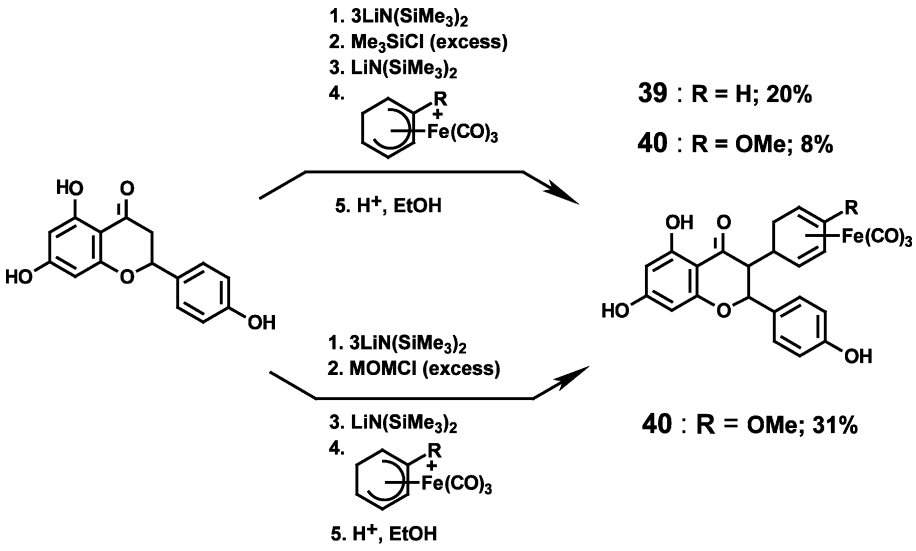


Scheme 8.

phenones, and have demonstrated that the nucleophile addition step is sufficiently fast to intercept flavanone-derived enolates prior to C-ring fragmentation. Metallated aromatic rings have also been employed as nucleophiles. Metallation adjacent to an oxazoline substituent, followed by trapping of the nucleophile with the organometallic electrophile proved effective, and lithium-for-halogen exchange next to an ether substituent also proved to be an effective strategy to gain access to suitable metallated nucleophilic precursors. In this way, a series of differently substituted aromatic rings carrying organometallic reporting groups have been prepared, and taken together with work described earlier [32], clear methodologies have been established for the selective attachment of organometalcarbonyl groups to either the rings A, B or C of the flavonoid skeleton.

4. Experimental

All reactions involving tricarbonyliron complexes were performed under an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware twice evacuated and filled with the nitrogen. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use as follows: diethyl ether (ether, Et_2O) and THF from sodium/benzophenone; dichloromethane and acetonitrile from calcium hydride. All reagents were purchased at highest commercial quality and used without further purification. Column chromatography was performed using Merck silica gels. TLC analyses were carried out on Merck aluminium-backed silica gel plates. Low resolution EI mass spectrometry (Kratos MS25 mass spectrometer) and elemental analyses were performed at the University of East



Scheme 9.

Anglia by Mr A.W.R. Saunders. Other mass spectra were measured at the EPSRC Mass Spectrometry Centre at University of Wales, Swansea. IR spectra were recorded on a Perkin–Elmer 1720X FTIR spectrometer as a thin film, unless solvent is specified. NMR spectra were recorded on Jeol FX270 (^{1}H, 270 MHz), or Jeol GX400 (^{1}H, 400 MHz) spectrometers. The operating frequency and solvent are indicated for each set of data in that order. Reference used was tetramethylsilane ($\delta = 0.00$). Compounds for biological testing were purified by reverse-phase HPLC using a Dynamax C18 column with gradient elution (methanol/water, flow rate—1.5 ml/min; programming (% water), 0–2 min 100 to 93%, 2–8 min 93 to 85%, 8–25 min 85 to 25%, 25–27 min 25 to 20%, 27–50 min 20%, 50–55 min 20 to 0%, 55–65 min 0%) and purity was checked by analytical HPLC employing a similar gradient.

4.1. Preparation and use of metallated arenes as nucleophiles with tricarbonyl(η^5-cyclohexadienyl)iron(1+) salts

*4.1.1. Tricarbonyl{(1,2,3,4-η)-5α-[2′-(4″,4″-dimethyloxazolin-2″-yl)-5′-methoxyphenyl]-1,3-cyclohexadiene}iron(0) (**5**) and tricarbonyl{(1,2,3,4-η)-2-methoxy-5α-[2′-(4″,4″-dimethyloxazolin-2″-yl)-5′-methoxyphenyl]-1,3-cyclohexadiene}iron(0) (**8**)*

*4.1.1.1. Preparation of 2-(4′-methoxyphenyl)-4,4-dimethyloxazoline (**3**).* Following a procedure based on a combination of literature methods [34], 4-methoxybenzoyl chloride (5 g, 29.4 mmol) in dichloromethane (25 ml) was added dropwise to 2-amino-2-methylpropanol (5.24 g, 58.8 mmol) with stirring at 0 °C. The precipitated solid was removed by filtration and the solvent was evaporated under reduced pressure. The residue was treated with $SOCl_2$ (15 ml, 206 mmol) with vigorous stirring. After the reaction was complete, the mixture was cooled and poured into ether. The precipitate was collected by filtration and hydrolysed with aq. NaOH (20%). The reaction mixture was extracted with ether (2 × 40 ml) and the extracts were dried over $MgSO_4$. A kugelrohr distillation produced 4.96 g (82%) of *2-(4′-methoxyphenyl)-4,4-dimethyloxazoline (**3**)* [34] as a clear oil which was used in step (4.1.1.2) without further purification. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.32 (6H, s, Me_2), 3.78 (3H, s, OMe), 4.03 (2H, s, $-CH_2-$), 6.85 (2H, d, $J = 8.6$ Hz, 3,5-H), 7.84 (2H, d, $J = 8.6$ Hz, 2-H, 6-H).

4.1.1.2. Metallation [35,45] and addition to tricarbonyl(cyclohexadienyl)iron(1+) salts. Following the procedure of Meyers [35] a solution of the oxazoline **3** (0.205 g, 1 mmol) in ether was treated with a hexane solution of *s*-BuLi (0.8 ml, 1 mmol) at −20 °C. The mixture was stirred for 4 h at 0 °C and then added to a stirred suspension of tricarbonyl[(1,2,3,4,5-η)-1,3-cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**4**) (0.225 g, 0.62 mmol) in dichloromethane cooled to −109 °C. The stirring continued for 2 h then water (50 ml) was added and the mixture was extracted with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with a mixture of hexane/ethyl acetate (3:1) as eluent afforded 200 mg (76%) of *tricarbonyl{(1,2,3,4-η)-5α-[2′-(4″,4″-dimethyloxazolin-2″-yl)-5′-methoxyphenyl]-1,3-cyclohexadiene}iron(0) (**5**)* as pale yellow oil. IR ν_{max}: 2964, 2917 (CH), 2042, 1967 (FeCO), 1653, 1646, 1607, 1558, 1507, 1282 cm^{-1}. MS (EI) *m/z* (relative intensity) 395 (M^+–CO, 6), 367 (M^+–2CO, 1), 339 (M^+–3CO, 24), 337 (63), 268 (90), 206 (100). Anal. Calc. for $C_{21}H_{21}NO_5Fe$: C 59.6, H

5.0, N 3.3. Found: C 59.9, H 5.0, N 3.2. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.33 (6H, s, Me, Me), 1.40 (1H, m, 6α-H), 2.39 (1H, ddd, $J = 15.2$, 11.2, 3.95 Hz, 6β-H), 3.15 (2H, m, 1-H, 4-H), 3.77 (3H, s, OMe), 3.99 (2H, s, OCH_2–), 4.41 (1H, dt, $J = 10.9$, 3.95 Hz, 5β-H), 5.44 (2H, m, 2,3-H), 6.64 (1H, dd, $J = 8.6$, 2.6 Hz, 4′-H), 6.80 (1H, d, $J = 2.6$ Hz, 6′-H), 7.51 (1H, d, $J = 8.6$ Hz, 2′-H).

Tricarbonyl{(1,2,3,4-η)-2-methoxy-5α-[2′-(4″,4″-dimethyloxazolin-2″-yl)-5′-methoxyphenyl]-1,3-cyclohexadiene}iron(0) (***8***) was prepared analogously as pale yellow oil from tricarbonyl[(1,2,3,4,5-η)-2-methoxy-1,3-cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**7**) (0.6 g, 1.52 mmol). Yield: 260 mg (38%). IR ν_{max}: 2962, 2896 (CH), 2041, 1961 (FeCO), 1653, 1607, 1569, 1485, 1226 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 425 (M^+–CO, 10), 397 (M^+–2CO, 3), 367 (100). HRMS (EI) Calc. for $M = C_{22}H_{23}NO_6Fe$. M^+–CO requires: 425.0926. Found: 425.0930. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.32 (6H, s, Me,Me), 1.52 (1H, ddd, $J =$ 14.85, 3.95, 2.9 Hz, 6α-H), 2.40 (1H, ddd, $J = 14.85$, 11.2, 3.95 Hz, 6β-H), 2.77 (1H, dd, $J = 6.6$, 3.6 Hz, 4-H), 3.38 (1H, m, 1-H), 3.65 (3H, s, 2-OMe), 3.78 (3H, s, 5′-OMe), 3.98 (2H, s, OCH_2-), 4.11 (1H, dt, $J = 10.9$, 3.6 Hz, 5β-H), 5.20 (1H, dd, $J = 6.6$, 2.3 Hz, 3-H), 6.64 (1H, dd, $J = 8.6$, 2.6 Hz, 4′-H), 6.78 (1H, d, $J = 2.6$ Hz, 6′-H), 7.51 (1H, d, $J = 8.6$ Hz, 2′-H).

*4.1.1.3. Attempted removal of the oxazoline protecting group from **5** and **8**.* A solution of the complex **5** (200 mg, 0.47 mmol) and methyl iodide (710 mg, 5 mmol) in acetone (20 ml) was heated at reflux until TLC showed no sign of the starting material (ca. 4 h). The volatiles were removed under reduced pressure and the residue was re-dissolved in dichloromethane (20 ml). The solution was cooled to −50 °C and then L-selectride (0.6 ml, 0.6 mmol) was added. The stirring continued for 1 h. The mixture was allowed to warm to −10 °C, ethanol solution of HCl (5 ml) was added and the mixture was stirred for an additional 1 h. After dilution with water (50 ml) and extraction with ether (3 × 30 ml), the combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel eluted with a mixture of hexane/ethyl acetate (3:1) afforded an inseparable mixture (60 mg) of the desired product, *tricarbonyl[(1,2,3,4-η)-5α-(2′-formyl-5′-methoxyphenyl)-1,3-cyclohexadiene]iron(0)* (***6***), with the starting oxazoline complex (3:2). Calculated yield of the product is 20% based on ^{1}H-NMR (taken in mixture with **5**): ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.48 (1H, dm, $J = 15.5$ Hz, 6α-H), 2.46 (1H, ddd, $J = 15.5$, 11.2, 3.95 Hz, 6β-H), 3.15 (2H, m, 1-H, 4-H), 3.84 (3H, s, OMe), 4.43 (1H, dt, $J = 11.2$, 3.6 Hz, 5β-H), 5.46 (2H, m, 2-H, 3-H), 6.77 (1H, dd, $J = 8.6$, 2.6 Hz, 4′-H), 6.89 (1H, d, $J = 2.6$ Hz, 6′-H), 7.66 (1H, d, $J = 8.6$ Hz, 2′-H), 10.00 (1H, s, CHO). This procedure, when used with **8**, was unsuccessful, and no products were isolated.

4.1.2. Tricarbonyl[(1,2,3,4-η)-5α-(2′-formyl-5′-t-butyldimethylsilyloxyphenyl)-1,3-cyclohexadiene]iron(0) (***10***)

4.1.2.1. Preparation of 2-bromo-4-hydroxybenzaldehyde [46]. Following a modification of the procedure of Hodgson [36], aq. KOH (30%, 160 ml) was added to 3-bromophenol (10.04 g, 58 mmol). The mixture was heated to 70–75 °C and then ethanol (5 ml) was added in one portion followed by dropwise addition of chloroform (28 ml, 0.35 mol) during 1 h at 75 °C. The reaction mixture was stirred for a further 3 h at that temperature. After cooling to room temperature (r.t.) and acidification (10 N HCl), most of the by-products were removed by steam distillation. The residue was cooled and the precipitate was separated by filtration. Column chromatography of the solid on silica gel with a mixture of hexane/ethyl acetate (2:1) as eluent afforded 1.75 g (15%) of *2-bromo-4-hydroxybenzaldehyde*. ^{1}H-NMR (270 MHz, acetone-d_6) δ: 6.89 (1H, ddd, $J = 8.6$, 2.3, 1.0 Hz, 5-H), 7.11 (1H, d, $J = 2.3$ Hz, 3-H), 7.76 (1H, d, $J = 8.6$ Hz, 6-H), 9.56 (1H, br s, OH), 10.12 (d, $J = 1.0$ Hz, CHO).

4.1.2.2. Protection of the hydroxy and aldehyde functions based on combinations of literature procedures for related compounds [47,48]. A solution of 4-hydroxybenzaldehyde (0.46 g, 3.77 mmol), *t*-BuMe_2SiCl (0.70 g, 4.64 mmol), and imidazole (0.8 g, 11.75 mmol) in DMF (20 ml) [47] was stirred at 65 °C for 6 h. Water was added followed by extraction with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel eluted with a mixture of hexane/ethyl acetate (5:1) afforded 525 mg (42%) of the target compound. (Unreacted starting material (430 mg) was also recovered.) This product (0.52 g, 1.65 mmol) was then heated at reflux with 1,2-dihydroxyethane (0.49 g, 7.9 mmol) in benzene (30 ml) in the presence of *p*-toluene sulfonic acid (0.1 g) for 6 h in an apparatus fitted with a Dean-Stark adapter [48]. The reaction mixture was concentrated, washed with an aq. sodium hydrogen carbonate solution and water, dried over $MgSO_4$ and then passed through a short silica gel column (3 × 2 cm) using hexane/ethyl acetate mixture (5:1) as eluent to afford 0.6 g (98%) of the desired product **9** as a light oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.18 (6H, s, Me_2Si), 0.98 (9H, s, *t*-BuSi), 4.05 (4H, m, -OCH_2CH_2O-), 6.02 (1H, s, O_2CH–), 6.76 (1H, dd, $J = 8.4$, 2.4 Hz, 5-H), 7.08 (1H, d, $J = 2.4$ Hz, 3-H), 7.45 (1H, d, $J = 8.4$ Hz, 6-H).

4.1.2.3. Metallation [49] and addition to the tricarbonyl(cyclohexadienyl)iron(1+) salt. A solution

of the protected compound **9** (0.59 g, 1.64 mmol) in ether (10 ml) was treated with a hexane solution of *n*-BuLi (1 ml, 1.55 mmol) at −78 °C. The mixture was stirred for 1 h and then added to a stirred suspension of tricarbonyl[(1,2,3,4,5-η)-1,3-cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**4**) (0.364 g, 1 mmol) in dichloromethane (20 ml), cooled to −78 °C. The stirring continued for 2 h. When the IR spectrum of the reaction mixture showed no sign of the starting salt, ethanolic HCl (5 ml) was added and the mixture was stirred at r.t. for an additional 0.5 h, diluted with water (50 ml) and extracted with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with a mixture of hexane/ethyl acetate (5:1) as eluent afforded 30 mg (7%) of *tricarbonyl[(1,2,3,4-η)-5α-(2′-formyl-5′-t-butyldimethylsilyloxyphenyl)-1,3-cyclohexadiene]iron(0)* (***10***) as a light-yellow viscous oil. IR ν_{max}: 2929, 2858 (CH), 2046, 1972 (FeCO), 1696 (formyl), 1598, 1561, 1490, 1258 cm^{-1}. MS (EI) *m/z* (relative intensity) 398 (M^+–2CO, 12), 270 (M^+–3CO, 38), 368 (100), 345 (19), 343 (19), 314 (8), 259 (37), 257 (36). HRMS (EI) Calc. for $M = C_{22}H_{26}O_5FeSi$. M^+–2CO requires: 398.1001. Found: 398.1001. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.24 (6H, s, $SiMe_2$), 0.97 (9H, s, Si–*t*-Bu), 1.50 (1H, m, 6α-H), 2.46 (1H, ddd, $J = 15.2$, 11.2, 3.95 Hz, 6β-H), 3.09 and 3.16 (2 × 1H, 2 × m, 1-H, 4-H), 4.41 (1H, dt, $J = 10.9$, 3.6 Hz, 5β-H), 5.46 (2H, m, 2-H, 3-H), 6.71 (1H, dd, $J = 8.6$, 2.3 Hz, 4′-H), 6.81 (1H, d, $J = 2.3$ Hz, 6′-H), 7.59 (1H, d, $J = 8.6$ Hz, 2′-H), 10.01 (1H, s, CHO).

4.1.3. Tricarbonyl[(1,2,3,4-η)-5α-(5′-formyl-2′-methoxyphenyl)-1,3-cyclohexadiene]iron(0) (***11***) *and tricarbonyl[(1,2,3,4-η)-2-methoxy-5α-(5′-formyl-2′-methoxyphenyl)-1,3-cyclohexadiene]iron(0)* (***12***)

4.1.3.1. Preparation of 3-bromo-4-hydroxybenzaldehyde. Using a modification of an established procedure [50], to a solution of 4-hydroxybenzaldehyde (6.84, 56 mmol) in dichloromethane/THF (80 ml, 3:1) at 0 °C, a solution of bromine (2.82 ml, 5.5 mmol) in dichloromethane (40 ml) was added dropwise during 2 h. The mixture then was stirred for 2 h at r.t. and left overnight. Work-up included subsequent washing with aq. sodium thiosulfate solution, water, drying over $MgSO_4$ and crystallisation from hexane/ethanol. Yield: 7.3 g (65%).

4.1.3.2. Protection of the hydroxy and aldehyde functions. A solution of 3-bromo-4-hydroxybenzaldehyde (2.0 g, 10 mmol), $(MeO)_2SO_2$ (3.7 g, 30 mmol), and K_2CO_3 (9.2 g, 70 mmol) in acetone (50 ml) was refluxed for 6 h. The solid was separated by filtration and then water was added followed by extraction with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product [51] (2.15 g, 10 mmol) was then heated at reflux with 1,2-dihydroxyethane (2.2 g, 36 mmol) in benzene (60 ml) in the presence of *p*-toluene sulfonic acid (0.1 g) for 6 h in an apparatus fitted with a Dean-Stark adapter [52]. The reaction mixture was concentrated, washed with aq. sodium hydrogen carbonate, and sodium bisulfate solutions (30%), and water, dried over $MgSO_4$, and then passed through a short silica gel column (3 × 2 cm) using a hexane/ethyl acetate mixture (5:1) with few drops of triethylamine as eluent to afford 1.66 g (64%) of the diprotected product. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 3.85 (3H, s, OMe), 4.02 (4H, m, $-OCH_2CH_2O-$), 5.69 (1H, s, $-O_2CH-$), 6.84 (1H, d, $J =$ 8.6 Hz, 5-H), 7.33 (1H, dd, $J = 8.25$, 2.0 Hz, 6-H), 7.63 (1H, d, $J = 2.0$, 2-H).

4.1.3.3. Metallation [53], addition to tricarbonyl(cyclohexadienyl)iron(1+) salts, and deprotection. A solution of the diprotected compound (0.52 g, 2 mmol) in THF (20 ml) was treated with a hexane solution of *n*-BuLi (1.5 ml, 2 mmol) at −78 °C. The mixture was stirred for 1 h, allowed to warm to −40 °C and then $CuBr \cdot Me_2S$ (0.206 g, 1 mmol) was added. The mixture was stirred for 1 h at −30 °C and after the solid dissolved, the solution was cooled to −78 °C and tricarbonyl[(1,2,3,4,5-η)-1,3-cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**4**) (0.3 g, 0.82 mmol) was added in one portion. The stirring continued for 2 h. The mixture was allowed to warm to −10 °C. An ethanol solution of HCl (5 ml) was added and the mixture was stirred for an additional 0.5 h. After dilution with water (50 ml) and extraction with ether (3 × 30 ml), the combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel eluted with a mixture of hexane/ethyl acetate (5:1) afforded a mixture of the desired product and the starting material. The latter was removed by kugelrohr distillation (100 °C, 0.1 Torr). The residue was repeatedly chromatographed to give 165 mg (57%) of *tricarbonyl[(1,2,3,4-η)-5α-(5′-formyl-2′-methoxyphenyl)-1,3-cyclohexadiene]iron(0)* (***11***) as a light-yellow viscous oil. IR ν_{max}: 2961, 2929, 2855 (CH), 2043, 1967 (FeCO), 1685 (C=O), 1599, 1578, 1511, 1259 cm^{-1}. MS (EI) *m/z* (relative intensity) 354 (M^+, 2), 326 (M^+–CO, 7.5), 298 (M^+–2CO, 93), 253 (100). HRMS (EI) Calc. for $C_{17}H_{14}O_5Fe$: 354.0191. Found: 354.0191. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.46 (1H, dt, $J = 15.2$, 3.6 Hz, 6α-H), 2.37 (1H, ddd, $J = 15.2$, 11.2, 3.95 Hz, 6β-H), 3.09 and 3.15 (2 × 1H, 2 × m, 1,4-H), 3.74 (1H, dt, $J = 11.2$, 3.6 Hz, 5β-H), 3.85 (3H, s, OMe), 5.48 (2H, m, 2-H, 3-H), 6.86 (1H, d, $J = 8.25$ Hz, 5′-H), 7.64 (dd, J = 8.25, 1.98 Hz, 1H, 6′-H), 7.71 (1H, d, $J = 2.0$ Hz, 2′-H), 9.82 (1H, s, CHO).

Tricarbonyl[(1,2,3,4-η)-2-methoxy-5α-(5′-formyl-2′-methoxyphenyl)-1,3-cyclohexadiene]iron(0) (***12***) was prepared analogously as pale yellow oil from tricarbon-

yl[(1,2,3,4,5-η) - 2 - methoxy - 1,3 - cyclohexadienyl]iron-(1+)hexafluorophosphate(1−) (**7**) (0.3 g, 0.76 mmol). Yield: 195 mg (67%). IR ν_{max}: 2960, 2930 (CH), 2041, 1961 (FeCO), 1690 (C=O), 1597, 1487, 1458, 1255 cm^{-1}. MS (EI) *m/z* (relative intensity) 384 (M^+, 1), 356 (M^+–CO, 7), 328 (M^+–2CO, 45), 300 (M^+–3CO, 34), 215 (100). HRMS (EI) Calc. for $C_{18}H_{16}O_6Fe$: 384.0296. Found: 384.0296. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.56 (1H, ddd, $J = 14.85$, 3.6, 2.3 Hz, 6α-H), 2.38 (1H, ddd, $J = 14.85$, 11.22, 3.96 Hz, 6β-H), 2.69 (1H, dd, $J = 6.60$, 3.63 Hz, 4-H), 3.39 (1H, m, 1-H), 3.53 (1H, dt, $J = 11.2$, 3.6 Hz, 5β-H), 3.66 (3H, s, 2-OMe), 3.85 (3H, s, 2′-OMe), 5.24 (1H, dd, $J = 6.6$, 2.0 Hz, 3-H), 6.85 (1H, d, $J = 8.25$ Hz, 3′-H), 7.64 (1H, dd, $J = 8.25$, 2.0 Hz, 4′-H), 7.70 (1H, d, $J = 2.0$ Hz, 6′-H), 9.83 (1H, s, CHO).

Use of the organolithium procedure as described in Section 4.1.2.3 gave the same products **11** and **12** but the yields were reduced to 9 and 15%, respectively.

4.1.4. 6-Hydroxy-4′-methoxy-2,4-bis-(methoxymethyloxy)-3′-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}chalcone ***14***

(a) Preparation of 6-hydroxy-2,4-bis-(methoxymethyloxy)acetophenone (**13**) [39]: By a method based on a combination of literature procedures [39], 2,4,6-trihydroxyacetophenone monohydrate (0.93 g, 5 mmol), *t*-BuOK (2.5 g, 22 mmol) and 18-crown-6 (0.2 g) were stirred in acetonitrile (30 ml) at r.t. Methoxymethyl chloride (2.3 ml, 30 mmol) was added in portions during 3 h. The mixture was stirred at r.t. for a further 3 h, and then water (20 ml) was added. The mixture was extracted with dichloromethane (3 × 30 ml). The combined dichloromethane extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with a mixture of hexane/ethyl acetate (3:1) as eluent afforded 0.72 g (56%) of the diprotected product (**13**). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.61 (3H, s, MeCO), 3.42 and 3.45 (2 × 3H, 2 × s, 2 × MeO), 5.22 and 5.25 (2 × 2H, 2 × s, $-CH_2O-$), 6.36 (2H, s, 3-H, 5-H), 14.05 (s, 1H, OH).

(b) Condensation with the benzaldehyde derivative: To a stirred solution of tricarbonyl[(1,2,3,4-η)-2-methoxy-5α-(5′-formyl-2′-methoxyphenyl)-1,3-cyclohexadiene]iron(0) **12** (230 mg, 0.6 mmol) and 6-hydroxy-2,4-bis-(dimethoxymethyloxy)acetophenone **13** (150 mg, 0.6 mmol) in 95% aq. ethanol (40 ml) at r.t. was added NaOH (750 mg, 19 mmol). The reaction mixture was heated at reflux for 2 h, stirred for further 3 h at r.t., and left overnight without stirring. Acidification with 0.1 N aq. HCl and extraction with ether (3 × 30 ml) afforded extracts which were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel eluted with mixtures of hexane/ethyl acetate (4:1 to 1:1) afforded 105 mg (28%) of *6-hydroxy-4′-methoxy-2,4-bis-(methoxymethyloxy)-3′-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}chalcone* (***14***) as a yellow viscous oil. IR ν_{max}: 3400 (OH), 2928 (CH), 2041, 1962 (FeCO), 1623 (C=O), 1583, 1558, 1486, 1424, 1346, 1253, 1222, 1149, 1111, 1082, 1059, 1021 cm^{-1}. HRMS (FAB) Calc. for $M = C_{30}H_{30}O_{11}Fe$. MH^+ requires: 623.1215. Found: 623.1199. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.62 (1H, m, 6″β-H), 2.36 (1H, m, 6″α-H), 2.70 (1H, dd, $J = 6.6$, 3.6 Hz, 4″-H), 3.41 (1H, m, 1″-H), 3.45, 3.51, 3.65, and 3.81 (4 × 3H, 4 × s, OMe), 3.55 (1H, m, 5″β-H), 5.16 and 5.27 (2 × 2H, 2 × s, OCH_2O), 5.20 (1H, dd, $J = 6.6$, 2.3, 3″-H), 6.21 and 6.29 (2 × 1H, 2 × d, $J = 2.6$ Hz, 3-H, 5-H), 6.78 (1H, d, $J = 8.2$ Hz, 5′-H), 7.36 (1H, d, $J = 2.3$ Hz, 2′-H), 7.40 (1H, dd, $J = 8.25$, 2.3, 6′-H), 7.77 (2H, m, –CH=CH–), 13.93 (1H, s, OH).

4.1.5. 2,4,6-Trihydroxy-4′-methoxy-3′-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}chalcone (***15***)

The chalcone (105 mg, 0.17 mmol) prepared as described in Section 4.1.4 was dissolved in ethanol (15 ml) and 4% H_2SO_4 in THF (20 ml) was added. The mixture was stirred for 4 h at r.t. Work-up as above followed by column chromatography on silica gel eluted with a mixture of hexane/ethyl acetate (2:1 to 1:1) afforded 64 mg (71%) of *2,4,6-trihydroxy-4′-methoxy-3′-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}chalcone* (**15**) as a yellow solid. IR ν_{max}: 3307 (OH), 2929, 2856 (CH), 2041, 1964, 1950 (FeCO), 1624 (C=O), 1600, 1559, 1509, 1560, 1351, 1253, 1222, 1171, 1115, 1079, 1029 cm^{-1}. HRMS (FAB) Calc. for $M = C_{26}H_{22}O_9Fe$. MH^+ requires: 535.0691. Found: 535.0710. ^{1}H-NMR (270 MHz, acetone-d_6) δ: 1.58 (1H, m, 6″β-H), 2.36 (1H, ddd, $J = 14.9$, 11.2, 4.0 Hz, 6″α-H), 2.79 (1H, dd, $J = 6.6$, 3.6 Hz, 4″-H), 3.41 (1H, m, 1″-H), 3.50 (1H, dt, $J = 11.2$, 3.6 Hz, 5″β-H), 3.71 and 3.82 (2 × 3H, 2 × s, 2″-OMe, 4′-OMe), 5.59 (1H, dd, $J = 6.6$, 2.3 Hz, 3″-H), 5.92 (2H, m, 6-H, 8-H), 6.92 (2H, d, $J = 8.5$ Hz, 5′-H), 7.47 (1H, dd, $J = 8.5$, 2.0 Hz, 6′-H), 7.55 (1H, d, $J = 2.0$ Hz, 2′ H), 7.62 and 8.11 (2 × 1H, 2 × d, $J = 15.95$ Hz, –CH=CH–), 14.02 (1H, s, OH).

4.1.5.1. 5,7-Dihydroxy-4′-methoxy-3′-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (***16***).

The deprotected chalcone **15** (60 mg, 0.11 mmol) prepared as described in Section 4.1.5 was dissolved in 80% aq. ethanol (20 ml) and pH of the solution was adjusted to 9 with ca. 0.1 mg of NaOH. The mixture was stirred for 6 h at r.t. Work-up as above was followed by column chromatography on silica gel eluted with mixtures of hexane/ethyl acetate (2:1 to 1:1) to afford 15 mg (25%) of *5,7-dihydroxy-4′-methoxy-3′-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}fla-*

*vanone (**16**)* as a pale-yellow viscous oil. Mixture of two diastereomers (1:1): IR ν_{max}: 3360 (OH), 2924, 2854 (CH), 2042, 1969 (FeCO), 1728, 1640, 1604, 1486, 1463, 1378, 1260, 1159, 1088, 1022 cm^{-1}. MS (FAB) *m/z* (relative intensity) 535 (MH^+, 2), 478 (M^+-2CO, 4), 450 (M^+-3CO, 3), 391 (4). ^{1}H-NMR (270 MHz, acetone-d_6) δ: 1.60 (2 × 1H, m, 6″β-H), 2.34 (2 × 1H, ddd, $J = 14.85$, 11.2, 3.6 Hz, 6″α-H), 2.70 and 2.72 (2 × 1H, dd, $J = 17.2$, 3.3 Hz, 3α-H), 2.77 and 2.78 (2 × 1H, 2 × dd, $J = 6.6$, 3.6 Hz, 4″-H), 3.15 and 3.16 (2 × 1H, 2 × dd, $J = 17.2$, 12.5 Hz, 3β-H), 3.41 (2 × 1H, m, 1″-H), 3.52 (2 × 1H, m, 5″β-H), 3.68 and 3.69 (2 × 3H, 2 × s, 2″-OMe), 3.79 (2 × 3H, s, 4′-OMe), 5.43 and 5.44 (2 × 1H, 2 × dd, $J = 12.5$, 2.95 Hz, 2-H), 5.56 (2 × 1H, m, 3″-H), 5.90 and 5.93 (2 × 2H, 2 × m, 6-H, 8-H), 6.91 (2 × 1H, d, $J = 8.2$ Hz, 5′-H), 7.30 (2 × 1H, dd, $J = 8.35$, 2.0 Hz, 6′-H), 7.39 and 7.40 (2 × 1H, 2 × d, $J = 2.0$ Hz, 2′-H), 12.13 (2 × 1H, s, 5-OH).

4.2. Alkylation of tricarbonyl(η^5-cyclohexadienyl)iron salts with acetophenone derivatives

4.2.1. Preparation of trimethylsilylenol ethers

*4.2.1.1. Preparation of 1-[2′,4′,6′-tris(trimethylsilyloxy)phenyl]-1-(trimethylsilyloxy)ethene (**26**).* (a) To a stirred solution of 2,4,6-trihydroxyacetophenone monohydrate (2.79 g, 15 mmol) and triethylamine (11 ml, 80 mmol) in Et_2O (300 ml) was added dropwise trimethylsilyl chloride (10 ml, 80 mmol). A heavy white precipitate was formed immediately, accompanied by a rise in temperature. The mixture was then heated at reflux for 7 h and allowed to stand overnight at r.t. The precipitate of the ammonium salt was removed by filtration and the filtrate was dried over $MgSO_4$. Removal of solvent at reduced pressure afforded 5.34 g (93%) of *2,4,6-tris(trimethylsilyloxy)acetophenone* as a pale yellow oil. IR ν_{max}: 2960, 1700, 1569, 1419, 1255, 1167, 1105, 1025 cm^{-1}. MS (EI) *m/z* (relative intensity) 384 (M^+, 3), 369 (100), 297 (17), 147 (3), 73 (23). Anal. Calc. for $C_{17}H_{32}O_4Si_3$: C, 53.13, H, 8.33. Found: C, 53.12, H, 8.62. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.22 (27H, s, 3 × $SiMe_3$), 2.35 (3H, s, Me), 5.95 (2H, s, 3-H, 5-H).

(b) The solution of this *tris*-trimethylsilyl derivative (1.81 g, 4.71 mmol) in THF (10 ml) was added dropwise via syringe to a solution of lithium diisopropylamide in THF (50 ml) prepared from 8 mmol of each *n*-BuLi (1.6 M in hexane) and diisopropylamine, and cooled to −78 °C. The resulting solution was stirred for 1.5 h at −78 °C, then trimethylsilyl chloride (1.2 ml, 9.4 mmol) was added and the mixture was stirred for a further 1.5 h at −78 °C. Evaporation of the solvent under reduced pressure gave a mixture of a yellow viscous liquid and a white precipitate of the ammonium salt. The precipitate was removed by filtration, washed with diethyl ether (3 × 30 ml) and the combined filtrate and washings were concentrated under vacuum. *1-[2′,4′,6′-Tris(trimethylsilyloxy)phenyl]-1-(trimethylsilyloxy)ethene (**26**)* was obtained as a pale yellow oil. Yield: 2.13 g (99%). IR ν_{max}: 2960, 1597, 1568, 1423, 1297, 1253, 1200, 1167, 1100, 1028 cm^{-1}. MS (EI) *m/z* (relative intensity) 456 (M^+, 26), 441 (99), 367 (75), 147 (21), 73 (100). Anal. Calc. for $C_{20}H_{40}O_4Si_4$: C, 52.63, H, 8.77. Found: C, 52.83, H, 8.98. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.23 (36H, s, $SiMe_3$), 4.20 and 4.57 (2 × 1H, 2 × s, $=CH_2$), 6.03 (2H, s, 3′-H, 5′-H).

*4.2.1.2. Preparation of 1-(2′,4′,6′-trimethoxyphenyl)-1-(trimethylsilyloxy)ethene (**21**).* Using the procedures described in Section 4.2.1.1b, 2,4,6-trimethoxyacetophenone [54] (1.05 g, 5 mmol) was converted into 1.4 g (99%) of 1-(2′,4′,6′-trimethoxyphenyl)-1-(trimethylsilyloxy)ethene [55] as a colourless oil. IR ν_{max}: 2958, 2839, 2360, 1696, 1605, 1496, 1465, 1414, 1340, 1280, 1251, 1227, 1206, 1187, 1159, 1130, 1014 cm^{-1}. MS (EI) *m/z* (relative intensity) 282 (M^+, 22), 267 (71), 251 (37), 237 (16), 210 (23), 195 (100), 180 (7), 165 (5), 152 (5), 137 (6), 109 (4), 89 (5), 73 (36). Anal. Calc. for $C_{14}H_{22}O_4Si$: C, 59.57, H, 7.80. Found: C, 59.53, H, 7.92. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.11 (9H, s, $SiMe_3$), 3.80 (9H, s, OMe), 4.28 and 4.72 (2 × 1H, 2 × s, $=CH_2$), 6.11 (2H, s, 3′-H, 5′-H).

4.2.2. General procedure for the use of trimethylsilylenol ethers with tricarbonyl(η^5-cyclohexadienyl)iron(1+) salts

To a stirred solution of the silylenol ether (1–2 mmol) in acetonitrile (5–10 ml) at r.t. was added the tricarbonyl(cyclohexadienyl)iron salt **4** or **7** (0.5–1 mmol). The reaction mixture was stirred for 48 h at r.t. and then aq. ammonium chloride (20 ml) was added. The mixture was shaken vigorously for 5 min and then extracted with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel with mixtures of hexane/ethyl acetate (9:1 to 4:1) as eluent.

4.2.3. General procedure for the preparation and use of lithium enolates with tricarbonyl(η^5-cyclohexadienyl)iron(1+) salts

To a solution of the acetophenone derivative (4 mmol) in Et_2O (10 ml) at −78 °C via syringe was added a solution of $LiN(SiMe_3)_2$ (4 mmol) in THF. The mixture was stirred for 1 h at that temperature and then added to a dichloromethane suspension (20 ml) of a tricarbonyl(cyclohexadienyl)iron salt **4** or **7** (0.5–1 mmol) at −78 °C. The reaction mixture was stirred for 1.5 h, allowed to warm to 0 °C and then water (20 ml) was added. The mixture was extracted with ether

(3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with mixtures of hexane/ethyl acetate (9:1 to 4:1) as eluent afforded a mixture of the target complex with the starting acetophenone. The latter was removed using kugelrohr and the product was once more purified by column chromatography.

4.2.4. General procedure for the preparation and use of copper-modified enolates with tricarbonyl(η^5-cyclohexadienyl)iron(1+) salts

$CuBr \cdot Me_2S$ (410 mg, 2 mmol) was added in one portion to a stirred solution of corresponding lithium reagent (4 mmol) prepared as described in Section 4.2.3, except that THF was used as solvent instead of ether. The mixture was stirred for 1.5 h at −15 to 0 °C and then added to a suspension of organoiron salts (0.5–1 mmol) in THF at −50 °C. Stirring continued for 1 h allowing the reaction mixture to warm to −10 °C. Work-up followed, as described above.

The following complexes were obtained by these procedures (see also Table 1):

Tricarbonyl[(1,2,3,4-η)-5α-benzoylmethyl-1,3-cyclohexadiene]iron(0) (***18***). Light-yellow viscous oil. IR ν_{max}: 3059, 2936, 2849 (CH), 2043, 1961 (FeCO), 1685 (C=O), 1597, 1581, 1448 cm^{-1}. MS (CI) *m/z* (relative intensity) 339 (MH^+, 0.8), 311 (MH^+–CO, 0.6). HRMS (CI) Calc. for $M = C_{17}H_{14}O_4Fe$. MH^+ requires: 339.0320. Found: 339.0320. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.22 (1H, dm, $J = 15.2$ Hz, 6β-H), 2.14 (1H, ddd, $J = 15.2$, 10.1, 3.8 Hz, 6α-H), 2.68 (1H, m, 5β-H), 2.76 (1H, dd, $J = 16.2$, 7.6 Hz, CH*H*–), 2.88 (1H, dd, $J = 16.2$, 5.6 Hz, –C*H*H–), 3.01 (1H, m, 1-H), 3.11 (1H, m, 4-H), 5.23 and 5.34 (2 × 1H, 2 × m, 2-H, 3-H), 7.39 (2H, m, 3′-H, 5′-H), 7.50 (1H, m, 4′-H), 7.85 (2H, d, $J = 7.25$ Hz, 2′-H, 6′-H).

Tricarbonyl[(1,2,3,4-η)-2-methoxy-5α-benzoylmethyl-1,3-cyclohexadiene]iron(0) (***20***). Light-yellow viscous oil. IR ν_{max}: 2043, 1967 (FeCO), 1685 (C=O), 1376, 1268, 1222 cm^{-1}. MS (EI) *m/z* (relative intensity) 368 (M^+, 1), 340 (M^+–CO, 4), 312 (M^+–2CO, 35), 284 (M^+–3CO, 100), 269 (31), 254 (15), 221 (15), 176 (45), 164 (39), 133 (80), 105 (78), 77 (48). Anal. Calc. for $C_{18}H_{16}O_5Fe$: C, 58.70, H, 4.35. Found: C, 58.51, H, 4.24. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.38 (1H, m, 6β-H), 2.18 (1H, m, 6α-H), 2.56 (1H, m, 5β-H), 2.81 (3H, m, $–CH_2–$ and 1-H), 3.30 (1H, m, 4-H), 3.63 (3H, s, OMe), 5.05 (1H, m, 3-H), 7.44–7.55 (3H, m, 3′-H, 4′-H, 5′-H), 7.89 (2H, m, 2′-H, 6′-H).

Tricarbonyl[1,2,3,4-η)-2-methoxy-5α-(2′,4′,6′-trimethoxybenzoylmethyl)-1,3-cyclohexadiene]iron(0) (**22**). Light-yellow solid, m.p. 122–123 °C. IR ν_{max}: 2942, 2841 (CH), 2039, 1962 (FeCO), 1696 (C=O), 1607, 1589, 1457, 1413 cm^{-1}. MS (EI) *m/z* (relative intensity) 402 (M^+–2CO, 3), 374 (M^+–3CO, 7), 266 (9), 219 (10), 206 (11), 195 (53). Anal. Calc. for $C_{21}H_{22}O_8Fe$: C 55.02, H 4.80. Found: C 54.82, H 4.70. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.34 (1H, ddd, $J = 14.85$, 2.65, 2.3 Hz, 6β-H), 2.05 (1H, ddd, $J = 14.85$, 10.1, 4.05 Hz, 6α-H), 2.42 (1H, m, 5β-H), 2.50 (1H, dd, $J = 15.2$, 8.15 Hz, –CH*H*–), 2.65 (1H, dd, $J = 5.2$, 5.6 Hz, –CH*H*–), 2.73 (1H, dd, $J = 6.6$, 3.3 Hz, 4-H), 3.26 (1H, m, 1-H), 3.58 (3H, s, 2-OMe), 3.72 (6H, s, 2′-OMe, 6′-OMe), 3.77 (3H, s, 4′-OMe), 4.99 (1H, dd, $J = 6.6$, 2.3 Hz, 3-H), 6.04 (2H, s, 3′-H, 5′-H).

Tricarbonyl[(1,2,3,4-η)-5α-(2′,4′,6′-trimethoxybenzoylmethyl)-1,3-cyclohexadiene]iron(0) (***24***). Light-yellow solid. IR ν_{max}: 3005, 2938, 2845 (CH), 2042, 1964 (FeCO), 1694 (C=O), 1607, 1589, 1495, 1458 cm^{-1}. MS (CI) *m/z* (relative intensity) 429 (MH^+, 6), 391 (74), 289 (21). HRMS (CI) Calc. for $M = C_{20}H_{20}O_7Fe$. MH^+ requires: 429.0637. Found: 429.0637. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.26 (1H, m, 6β-H), 2.07 (1H, m, 6α-H), 2.60 (3H, m, 5β-H, $–CH_2–$), 3.02 (1H, m, 1-H), 3.15 (m, 1H, 4-H), 3.71 (6H, s, 2′,6′-OMe), 3.77 (3H, s, 4′-OMe), 5.20 and 5.32 (2 × 1H, 2 × m, 2-H, 3-H), 6.09 (2H, s, 3′,5′-H).

4.2.5. Preparation of tricarbonyl[(1,2,3,4-η)-2-methoxy-5α-(2′,4′,6′-trihydroxybenzoylmethyl)-1,3-cyclohexadiene]iron(0) (*30*) using the lithium enolate method

A solution of the bis-MOM derivative **13** [39] prepared as described in Section 4.1.4a (0.2 g, 0.8 mmol) in dry THF (20 ml) at −78 °C was treated with $LiN(SiMe_3)_2$ in THF (0.8 ml, 0.8 mmol) and after 10 min with trimethylsilyl chloride (0.2 ml, 1.5 mmol). The resulting solution was stirred for 0.5 h, then solvent was removed under reduced pressure and ether (10 ml) was added to the residue. The mixture was cooled to −78 °C. $LiN(SiMe_3)_2$ in THF (0.8 ml, 0.8 mmol) was added and the mixture was stirred for 1 h at −78 °C. The resulting suspension was first diluted with dichloromethane (50 ml) keeping temperature at −78 °C and then tricarbonyl[(1,2,3,4,5-η)-2-methoxy-1,3-cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**7**) (0.25 g, 0.63 mmol) was added in one portion. The mixture was stirred for 2 h and the allowed to warm to r.t. A solution of HCl in methanol (1 N, 15 ml) was added and stirring continued for 0.5 h. Then water (50 ml) was added and the mixture was extracted with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with a mixture of hexane/ethyl acetate (3:1) as eluent afforded 0.14 g (53%) of *tricarbonyl[(1,2,3,4-η)-2-methoxy-5α-(2′,4,′6′-trihydroxybenzoylmethyl)-1,3-cyclohexadiene]iron(0)* (***30***) as a light-yellow viscous oil. IR ν_{max}: 3325 (OH), 2936 (CH), 2043, 1965 (FeCO), 1636 (C=O), 1605, 1525, 1486, 1458 cm^{-1}. MS (EI) *m/z* (relative intensity) 360 (M^+–2CO, 1), 332 (M^+–3CO, 1), 279 (5), 260 (4), 206 (11), 168 (36).

HRMS Calc. for M = $C_{18}H_{16}O_8Fe$. M^+–2CO requires: 360.0296. Found: 360.0296. ^{1}H-NMR (270 MHz, acetone-d_6) δ: 1.43 (1H, dt, J = 14.85, 2.65 Hz, 6β-H), 2.10 (1H, m, 6α-H), 2.53 (1H, m, 5β-H), 2.88 (1H, dd, J = 6.6, 3.3 Hz, 4-H), 2.89 (1H, dd, J = 16.5, 8.25 Hz, –C*H*H–), 3.12 (1H, dd, J = 16.5, 5.6 Hz, –C*H*H–), 3.37 (1H, m, 1-H), 3.69 (3H, s, 2-OMe), 5.39 (1H, dd, J = 6.6, 2.3 Hz, 3-H), 5.92 (2H, s, 3′-H, 5′-H).

4.3. Alkylation of tricarbonyl(η^5-cyclohexadienyl)iron salts with trimethoxyflavanone derivatives

4.3.1. Preparation of 4′,5,7-trimethoxyflavanone **34**

By a combination of literature methods [56] a mixture of 4′,5,7-trihydroxyflavanone [57] (2.18 g, 8 mmol), dimethyl sulfate (10 ml, 0.1 mol) and potassium carbonate (27.6 g, 0.2 mol) in acetone (100 ml) was heated at reflux for 24 h. The solid was separated by filtration. The filtrate was evaporated and water (50 ml) was added to the residue, which was extracted with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with a mixture of hexane/ethyl acetate (2:1) as eluent afforded 1.91 g (76%) of *4′,5,7-trimethoxyflavanone* (***34***) [42,57] as a pale-yellow solid, m.p. 123–125 °C ([57] 128 °C; [58] 125 °C) ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.71 (1H, dd, J = 16.5, 2.95 Hz, 3β-H), 2.99 (1H, dd, J = 16.5, 13.2 Hz, 3β-H), 3.76 and 3.78 (2 × 3H, 2 × s, 5-OMe, 7-OMe), 3.84 (3H, s, 4′-OMe), 5.30 (1H, dd, J = 13.2, 2.95 Hz, 2-H), 6.04 and 6.09 (2 × 1H, 2 × d, J = 2.3 Hz, 6-H, 8-H), 6.89 (2H, d, J = 8.6 Hz, 3′-H, 5′-H), 7.34 (2H, d, J = 8.6 Hz, 2′-H, 6′-H).

4.3.2. Addition to the tricarbonyl(cyclohexadienyl)iron(1+) salt: general procedure A (lithium enolate method)

To a stirred solution of 4′,5,7-trimethoxyflavanone [42] (0.48 g, 1.5 mmol) cooled to −110 °C, a THF solution of $LiN(SiMe_3)_2$ (1.5 ml, 1.5 mmol) was added. The mixture was stirred for 1 h, and then tricarbonyl-[(1,2,3,4,5-η)-1,3-cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**4**) (0.25 g, 0.69 mmol) was added in one portion. The stirring continued for 2 h, and then water (20 ml) was added. The mixture was extracted with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with mixtures of hexane/ethyl acetate (4:1 to 2:1) as eluent afforded in order of elution 90 mg (23%) of *2,4,4′-trimethoxy-6-hydroxy-5-{tricarbonyl[(1″,2″,3″,4″-η)-1″,3″-cyclohexadien-5″α-yl]iron(0)}chalcone* (***37***) and 250 mg (65%) of *4,5,7-trimethoxy-3-{tricarbonyl[1″,2″,3″,4″-η)-1″,3″-cyclohexa-5″α-dienyl]iron(0)}flavanone* (***36***).

The following complexes were obtained by this procedure (see also Table 1):

Chalcone (***35***). Yellow-orange crystals: m.p. 160–162 °C. IR ν_{max}: 3430 (OH), 2925, 2846 (CH), 2038, 1964, 1950 (FeCO), 1627 (C=O), 1605, 1559, 1511 cm^{-1}. Anal. Calc. for $C_{27}H_{24}O_8Fe$: C 60.89, H 4.55. Found: C 61.05, H 4.41. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.87 (2H, m, 6″-CH_2), 2.91 (1H, m, 1″-H), 3.15 (1H, m, 4″-H), 3.80, 3.84, and 3.88 (3 × 3H, 3 × s, 2-OMe, 4-OMe, 4′-OMe), 3.96 (1H, m, 5″β-H), 5.36 (2H, m, 2″-H, 3″-H), 5.90 (1H, s, 3-H), 6.87 (2H, d, J = 8.8 Hz, 3′-H, 5′H), 7.50 (2H, d, J = 8.8 Hz, 2′-H, 6′-H), 7.69 (2H, s, –CH=CH–), 14.22 (1H, s, OH).

Flavanone (***36***). Pale-yellow viscous oil. Mixture of two diastereoisomers (1:1): IR ν_{max}: 3007, 2937, 2842 (CH), 2043, 1963 (FeCO), 1735 (C=O), 1670, 1608, 1575, 1514, 1457 cm^{-1}. HRMS (FAB) Calc. for M = $C_{27}H_{24}O_8Fe$. M^+ + Na requires: 555.0718. Found: 555.0704. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.55 and 1.65 (2 × 1H, 2 × dm, J = 15.3 Hz, 6″β-H), 1.87 and 2.19 (2 × 1H, 2 × ddd, J = 15.2, 10.55, 3.95 Hz, 6″α-H), 2.45 (2 × 1H, m, 3-H), 2.51 and 2.63 (2 × 1H, 2 × m, 5″β-H), 2.85, 3.02, 3.05, and 3.23 (4 × 1H, 4 × m, 1″-H, 4″-H), 3.67, 3.71 (2 × 3H, 2 × s, 5-OMe), 3.75, 3.76, 3.77, and 3.79 (4 × 3H, 4 × s, 4′-OMe, 7-OMe), 5.32 (2 × 2H, m, 2″-H, 3″-H), 5.33 and 5.59 (2 × 1H, 2 × m, 2-H), 5.95 and 5.98 (2 × 1H, 2 × d, J = 2.3 Hz, 6-H), 6.05 (2 × 1H, m, 8-H), 6.73 and 6.75 (2 × 2H, 2 × d, J = 8.9 Hz, 3′-H, 5′-H), 7.11 and 7.17 (2 × 2H, 2 × d, J = 8.9 Hz, 2′-H, 6′-H).

When the reaction of the lithium enolate of 4′,5,7-trimethoxyflavanone with organoiron salt **7** was carried out at −78 °C, the only product isolated was chalcone **38** (yield 10%). For characterisation of **38**, see Section 4.3.3.

4.3.3. Addition to the tricarbonyl(cyclohexadienyl)iron(1+) salt: general procedure B (copper-modified enolate method)

The solution of 4′,5,7-trimethoxyflavanone [42] (0.63 g, 2.0 mmol) in THF (5 ml) was added dropwise via syringe to a solution of lithium diisopropylamide in THF (20 ml) prepared from 2.1 mmol of each *n*-BuLi (1.5 M in hexane) and diisopropylamine, and cooled to −78 °C. The mixture was stirred for 15 min. Afterwards $CuBr \cdot Me_2S$ (0.208 g, 1 mmol) was added in one portion and stirring continued for further 1 h at −78 °C. Then tricarbonyl[(1,2,3,4,5-η)-2-methoxy-1,3-cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**7**) (0.2 g, 0.5 mmol) was added also in one portion and the mixture was gently warmed to r.t. After 1 h, aq. ammonium chloride (20 ml) was added. The mixture was extracted with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with the dichloromethane as eluent afforded in order of

elution 453 mg (72%) of *2,4,4′-trimethoxy-6-hydroxychalcone* and 78 mg (28%) *2,4,4′-trimethoxy-6-hydroxy-5-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexa-5″α-dienyl]iron(0)}chalcone* (***38***).

The following products were obtained by this procedure (see also Table 1):

2,4,4′-Trimethoxy-6-hydroxychalcone [59]. Orange crystals: m.p. 110–112 °C ([57] 113–114 °C). IR ν_{max}: 3055, 2987, 2306, 1624, 1561, 1512, 1423, 1344, 1266, 1218, 1173, 1159, 1114, 1033 cm^{-1}. MS (EI) *m/z* (relative intensity) 314 (M^+, 2), 290 (3), 262 (7), 234 (35), 220 (6), 205 (4), 164 (100), 135 (92), 108 (17), 92 (13), 77 (30). Anal. Calc. for $C_{18}H_{18}O_5$: C 68.79, H 5.73. Found: C 68.65, H 5.62. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 3.80, 3.84 and 3.88 (3 × 3H, 3 × s, 2-OMe, 4-OMe, 4′-OMe), 5.92 and 6.07 (2 × 1H, 2 × d, $J = 2.0$ Hz, 3-H, 5-H), 6.90 (2H, d, $J = 8.60$ Hz, 3′-H, 5′-H), 7.53 (2H, d, $J = 8.6$ Hz, 2′-H, 6′-H), 7.77 (2H, s, –CH=CH–), 14.47 (1H, s, OH).

2,4,4′-Trimethoxy-6-hydroxy-5-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-l″,3″-cyclohexadien-5′′α-yl]iron(0)}chalcone (***38***). Orange viscous oil. IR ν_{max}: 2939, 2037, 1960 (FeCO), 1606 (C=O), 1561, 1512, 1487, 1466, 1423, 1326, 1305, 1290, 1256, 1222, 1173, 1120, 1073, 1026 cm^{-1}. HRMS (FAB) Calc. for $M = C_{28}H_{26}O_9Fe$. MH^+ requires: 563.1004. Found: 563.1004. Anal. Calc. for $C_{28}H_{26}O_9Fe$: C 59.79, H 4.63. Found: C 60.02, H 4.61. ^{1}H-NMR (90 MHz, $CDCl_3$) ?δ: 2.03 (2H, m, 6″-CH_2), 2.56 (1H, m, 4″-H), 3.40 (1H, m, 1″-H), 3.59 (3H, s, 2″-OMe), 3.75 (1H, m, 5″β-H), 3.83, 3.87, and 3.92 (3 × 3H, 3 × s, 2-OMe, 4-OMe, 4′-OMe), 5.09 (1H, m, 3″-H), 5.93 (1H, s, 3-H), 6.90 (2H, d, $J =$ 8.7 Hz, 3′-H, 5′-H), 7.53 (2H, d, $J = 8.7$ Hz, 2′,6′-H), 7.73 (2H, s, CH = CH–), 14.31 (1H, s, OH).

4.3.4. Addition to the tricarbonyl(cyclohexadienyl)iron(1+) salt: general procedure C (sodium enolate method)

To a solution of 4′,5,7-trimethoxyflavanone (0.746 g, 2.4 mmol) in THF (50 ml) cooled to −78 °C was added NaH (68 mg, 2.9 mmol) in one portion. The mixture was stirred for 1 h at −78 °C and then tricarbonyl[(1,2,3,4,5-η)-2-methoxy-1,3-cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**7**) (0.946 g, 2.4 mmol) was added also in one portion. After 15 min at −78 °C, the mixture was gently warmed to r.t. Stirring continued overnight. The reaction mixture was worked up as described in Section 4.4.3. Column chromatography on silica gel with the dichloromethane as eluent afforded this time only *2,4,4′-trimethoxy-6-hydroxy-5-(tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}chalcone* (**38**). Yield 306 mg (23%). Spectroscopic details as shown in Section 4.3.3.

4.4. Alkylation of tricarbonyl(η^5-cyclohexadienyl)iron salts with tris(trimethylsilyloxy)flavanone derivatives

4.4.1. Preparation of 4,4′,5,7-tetra(trimethylsilyloxy)-3,4-didehydroflavanane (*31*)

A stirred solution of 4′,5,7-trihydroxyflavanone (**1**) (0.41 g, 1.5 mmol) in THF (20 ml) was treated with THF solution of $LiN(SiMe_3)_2$ (6 ml, 6 mmol) at −78 °C. The thick suspension was stirred for 1.5 h at −78 °C. Trimethylsilyl chloride (1 ml, 7.9 mmol) was added and the mixture was stirred for a further 1.5 h at −78 °C. Volatiles were removed under reduced pressure. The residue was redissolved in diethyl ether, dried over $MgSO_4$ and concentrated under vacuum. *4,4′,5,7-Tetra(trimethylsilyloxy)-3,4-didehydroflavanane* (***31***) was obtained as an orange oil (0.67 g, 79%). IR ν_{max}: 2961, 2902, 1560, 1510, 1255, 1168, 1097, 1021 cm^{-1} MS (EI) *m/z* (relative intensity) 560 (M^+, 0.3), 545 (3), 488 (12), 473 (15), 416 (49), 296 (10), 251 (14), 224 (14), 192 (52), 179 (100), 147 (88), 73 (73). Anal. Calc. for $C_{27}H_{44}O_5Si_4$: C, 57.86, H, 7.86. Found: C, 58.15, H, 7.61. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.25 (36H, s, $SiMe_3$), 6.02 (2H, s, 6-H, 8-H), 6.67–7.50 (6H, m, 2-H, 3-H, 2′-H, 3′-H, 5′-H, 6′-H).

4.4.2. Attempted use of the trimethylsilylenol ether method with the flavanone derivative

To a stirred solution of the trimethylsilylenol ether (**31**) (0.56 g, 1 mmol) in acetonitrile (20 ml) at r.t. was added the tricarbonyl(cyclohexadienyl)iron salt **4** or **7** (0.5–1 mmol). The reaction mixture was stirred for 48 h at r.t. and then aq. ammonium chloride (20 ml) was added. The mixture was shaken vigorously for 5 min and then extracted with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with mixtures of hexane/ethyl acetate (4:1 to 2:1) as eluent. Only the starting flavanone **1** was recovered in either case.

4.4.3. One-pot protection, enolate generation, reaction with the tricarbonyl(cyclohexadienyl)iron(1+) salt, and deprotection

4.4.3.1. Using trimethylsilyl protecting groups. A stirred suspension of 4′,5,7-trihydroxyflavanone (**1**) (0.545 g, 2 mmol) in THF (20 ml) was treated with a THF solution of $LiN(SiMe_3)_2$ (6 ml, 6 mmol) at −78 °C. A thick precipitate was formed. After 0.5 h, trimethylsilyl chloride (0.7 g, 6.5 mmol) was added to form a thinner suspension. The mixture was stirred for an additional 0.5 h and then volatiles were removed under reduced pressure to afford the crude tri-protected derivative [60]. The residue was re-suspended in dichloromethane (30 ml) and cooled to −10 °C. A THF solution of $LiN(SiMe_3)_2$ (2 ml, 2 mmol) was added. The mixture

was stirred for 0.5 h, and then tricarbonyl[(1,2,3,4,5-η)-1,3-cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**4**) (0.25 g, 0.69 mmol) was added in one portion. The stirring continued for 2 h allowing the mixture to warm to r.t. The mixture was treated with 1 N HCl in MeOH/H_2O (10:1, 3 ml) at r.t. for 20 min and then water (20 ml) was added. The resulting mixture was extracted with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with mixtures of hexane/ethyl acetate (4:1 to 2:1) as eluent afforded 65 mg (20%) of *4′,5,7-trihydroxy-3-{tricarbonyl-[(1″,2″,3″,4″-η)-1″,3″-cyclohexa-5″α-dienyl]iron(0)}-flavanone* (***39***) as a pale-yellow viscous oil. Mixture of two diastereoisomers (5:4): IR ν_{max}: 3390 (OH), 2927 (CH), 2045, 1967 (FeCO), 1701, 1636, 1629, 1602, 1517, 1457 cm^{-1}. HRMS (FAB) Calc. for $M = C_{27}H_{24}O_8Fe$. $M^+ - 3CO$ requires: 406.0503. Found: 406.0493. ^{1}H-NMR (270 MHz, acetone-d_6) δ: 1.38 and 1.58 (2 × 1H, 2 × dm, $J = 15.5$ Hz, 6″β-H), 1.68 and 1.85(2 × 1H, 2 × m, 6″α-H), 2.29 and 2.41 (2 × 1H, 2 × m, 5″β-H), 2.62 and 2.75 (2 × 1H, 2 × m, 3-H), 2.88, 2.95, 3.01, and 3.09 (4 × 1H, 4 × m, 1″-H, 4″-H), 4.95, 5.28, 5.32, and 5.34 (4 × 1H, 4 × m, 2″-H,3″-H), 5.60 (2 × 1H, m, 2-H), 5.91, 5.93, 5.98, and 6.03 (4 × 1H, 4 × d, $J = 2.0$ Hz, 6-H, 8-H), 6.85 and 6.88 (2 × 2H, 2 × d, $J = 8.6$ Hz, 3′-H, 5′-H), 7.26 and 7.31 (2 × 2H, 2 × d, $J = 8.6$ Hz, 2′-H, 6′-H), 12.24 and 12.27 (1H, s, 5-OH).

4′,5,7-Trihydroxy-3-{tricarbonyl[(1″,2″,3″,4″-η)-2″-methoxy-1″,3″-cyclohexadien-5″α-yl]iron(0)}flavanone (***40***) was prepared analogously as pale-yellow oil from tricarbonyl[(1,2,3,4,5-η) - 2 - methoxy - 1,3 - cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**7**) (0.25 g, 0.63 mmol). Yield: 25 mg (8%). Mixture of two diastereoisomers (1:1): IR ν_{max}: 3384 (OH), 2927 (CH), 2044, 1964 (FeCO), 1701, 1636, 1620, 1597, 1518, 1485 cm^{-1}. HRMS (FAB) Calc. for $M = C_{25}H_{20}O_9Fe$. MH^+ requires: 521.0534. Found: MH^+ 521.0500. ^{1}H-NMR (270 MHz, acetone-d_6) δ: 1.72 and 1.90 (2 × 1H, 2 × ddd, $J = 14.9$, 3.95, 2.3 Hz, 6″β-H), 1.86 and 2.16 (2 × 1H, 2 × m, 6″α-H), 2.43 and 2.57 (2 × 1H, 2 × m, 5″β-H), 2.59 (1H, m, 3-H), 2.69 and 2.82 (2 × 1H, 2 × dd, $J = 6.3$, 3.6 Hz, 4″-H), 3.29 (2 × 1H, 2 × m, 1″-H), 3.59 and 3.66 (2 × 3H, 2 × s, 2″-OMe), 5.03 and 5.47 (2 × 1H, 2 × dd, $J = 6.6$, 2.3 Hz, 3″-H), 5.45 and 5.78 (2 × 1H, 2 × d, $J = 4.6$ and 4.3 Hz, respectively, 2-H), 5.81, 5.85, 5.89, and 5.90 (4 × 1H, 4 × m, 6-H, 8-H), 6.74 (4H, d, $J = 8.6$ Hz, 3′,5′-H), 7.14 and 7.17 (2 × 2H, 2 × d, $J = 8.59$ Hz, 2′,6′-H), 11.93 and 12.06 (2 × 1H, 2 × s, 5-OH).

4.4.3.2. Using methoxymethyloxy protecting groups in a two step sequence.

4.4.3.2.1. Preparation of 4′,5,7-tris(methoxymethyloxy)flavanone. A stirred suspension of 4′,5,7-trihydroxyflavanone (1.09 g, 4 mmol) in THF (200 ml) was treated with a THF solution of $LiN(SiMe_3)_2$ (12 ml, 12 mmol) at −78 °C to form a thick slurry, which was stirred for 1.5 h −78 °C. The mixture was warmed to 0 °C and methoxymethyl chloride (2 ml, 26.3 mmol) was added dropwise. Stirring continued for 2 h at r.t. and then volatiles were removed under reduced pressure. Water (20 ml) was added to the residue which was extracted with ether (3 × 30 ml). Combined extracts were dried over $MgSO_4$. Column chromatography on silica gel with a mixture of hexane/ethyl acetate (4:1) as eluent afforded 0.7 g (43%) of *4′,5,7-tris(methoxymethyloxy)flavanone* as a light yellow solid. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.64 (1H, dd, $J = 16.7$, 3.95 Hz, 3α-H), 3.00 (1H, dd, $J = 16.7$, 12.1 Hz, 3β-H), 3.43, 3.44, and 3.45 (3 × 3H, 3 × s, 4′-OMe, 5-OMe, 7-OMe), 5.13, 5.15, and 5.16 (3 × 2H, 3 × s, $-OCH_2O-$), 5.33 (1H, dd, $J =$ 12.1, 3.95 Hz, 2-H), 6.37 (2H, m, 6-H, 8-H), 7.03 (2H, d, $J = 8.55$ Hz, 3′-H, 5′-H), 7.34 (2H, d, $J = 8.6$ Hz, 2′-H, 6′-H). This product was used in the next step without further purification.

4.4.3.2.2. Enolate generation, addition to the tricarbonyl(cyclohexadienyl)iron(1+) salt, and deprotection. To a stirred solution of the crude 4′,5,7-*tris*(methoxymethyloxy)flavanone (0.467 g, 1.16 mmol) prepared as described above, and cooled to −109 °C, a THF solution of $LiN(SiMe_3)_2$ (1.2 ml, 1.2 mmol) was added. The mixture was stirred for 1 h, and then tricarbonyl[(1,2,3,4,5 - η) - 2 - methoxy - 1,3 - cyclohexadienyl]iron(1+) hexafluorophosphate(1−) (**7**) (0.3 g, 0.76 mmol) was added in one portion. The stirring continued for 2 h, and then water was added. The mixture was extracted with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with mixtures of hexane/ethyl acetate (4:1 to 2:1) as eluent afforded 198 mg (40%) of an intermediate which was treated with 1 N HCl in MeOH/H_2O (10:1, 3 ml) at r.t. for 20 min. Then water was added. The resulting mixture was extracted with ether (3 × 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel with mixtures of hexane/ethyl acetate (4:1 to 2:1) as eluent afforded 122 mg (77 or 31% by calculation based on the starting organoiron salt) of *4′,5,7-trihydroxy-3-[tricarbonyl[(1′,2′,3′,4′-η)-2′-methoxy-1′,3′-cyclohexadien-5′α-yl]iron(0)}flavanone* (***40***). Spectroscopic details are shown in Section 4.4.3.1.

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