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# Tricarbonyliron(0) complexes of bio-derived $\eta^4$ cyclohexadiene ligands: An approach to analogues of oseltamivir

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ABSTRACT

We have prepared novel $[\eta^4]$ and $[\eta^5]^+$ tricarbonyliron complexes from an unusual enantiopure cyclohexadiene ligand that possesses a quaternary stereocentre; this in turn is prepared through biotransformation of an aromatic ring. The cyclohexadiene ligand initially possessed two hydroxyl groups, both of which could be substituted with other functionality by means of an overall $[\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4]$ sequence. From six novel tricarbonyliron complexes which have been prepared, three have been characterised by x-ray crystallography. The reaction sequence we describe is potentially of relevance to the synthesis of analogues of the anti-influenza drug oseltamivir. In addition, the failure of an attempted addition of a bulky nitrogen nucleophile to an $[\eta^5]^+$ complex sheds light on the limits of reactivity for such additions. Thus, two bulky nucleophiles which are each known to add successfully to unencumbered $[\eta^5]^+$ complexes seemingly cannot be added sequentially to adjacent positions on the cyclohexadiene ligand.



## 1. Introduction

Dihydroxylation of an aromatic ring using a microorganism is a useful synthetic method, insofar as such a transformation is very difficult to achieve by conventional methodology [1]. This biotransformation has been known since 1968 [2] and the cyclohexadiene-*cis*-diol products of this reaction have found application in many branches of synthesis [3]. There are now many hundreds of these *cis*-diols which have been reported, and several of them are commercially available in significant quantities from suppliers such as Almac group. The selectivity of the dihydroxylation process has been extensively studied, and as shown in Scheme 1, a trend has been discerned [4]. In the majority of cases, metabolism of a monosubstituted arene **1** will afford the product **2**, having the stereochemistry shown, arising from dihydroxylation in the *ortho* and *meta* positions (Scheme 1a). In contrast, certain organisms [5] are able to metabolise benzoic acid **3** to give the product **4**, a process exhibiting not only complementary regioselectivity (*i.e. ipso* and *ortho* dihydroxylation) but also the opposite sense of absolute stereoinduction (Scheme 1b). Unlike *cis*-diols of type **2**, *cis*-diol **4** possesses a quaternary centre, which makes **4** (and substituted variants thereof) [6] a particularly useful chiral pool starting material [3a]. *cis*-Diol **4** has seen uses in the synthesis of natural products [7], carbohydrates [8], drug candidates [9], and various novel architectures [10].

The organometallic chemistry of such *cis*-diols has been most extensively explored for iron. Complexation of a diene as a $[\eta^4]$ tricarbonyliron(0) complex can serve not only as a "protecting group" for the diene, but also as a synthetically enabling transformation that allows access to new reactivity that is not available for the uncomplexed diene [11]. For *cis*-diols of type **2**, it has been demonstrated that treatment with $Fe_2(CO)_9$ indeed leads to the formation of the $[\eta^4]$ tricarbonyliron(0) complex of the diene [12]. As shown in Scheme 2a, of the two possible diastereomeric products which could be formed, only the product with the diol *endo* is obtained (*i.e.* the iron coordinates to the face of the cyclohexadiene ring which bears the hydroxyl groups). This trend has been shown to be consistent for various diene substituents (**2** → **5**) and also

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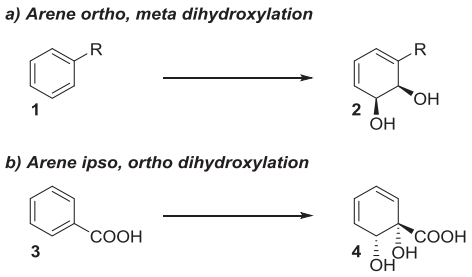
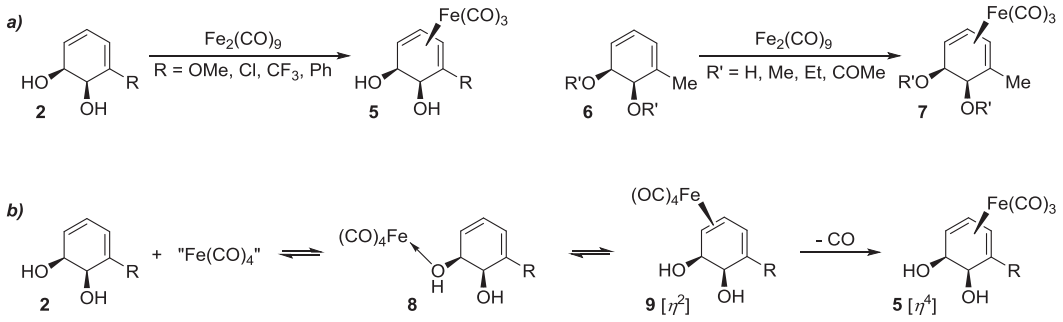



**Scheme 1.** Regio- and stereoselectivity of dioxygenase enzymes.

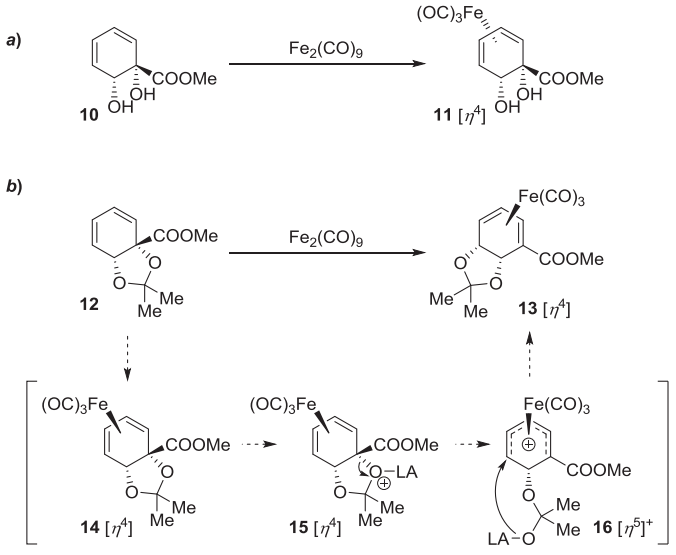
diol dominates over pre-coordination to the ester (Scheme 3a) [14a]. In contrast, when the diol is protected as an acetonide (as in **12**), a product **13** may be isolated in which the (masked) diol is now *exo* (Scheme 3b) [14b]. Unexpectedly, **13** was the product of a "clockwise" acetonide migration, which we propose occurs via an $[\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4]$ sequence [16]. Thus, the initially formed $[\eta^4]$ complex **14** coordinates an unidentified Lewis acidic species to give $[\eta^4]$ complex **15**, in which the acetonide oxygen has been rendered cationic (and hence a good leaving group). Extrusion of this leaving group gives $[\eta^5]^+$ complex **16**, which bears a tethered nucleophile. Such $[\eta^5]^+$ cyclohexadienyl complexes are known readily to undergo addition of nucleophiles at the termini of the dienyl ligand




**Scheme 2.** Facial selectivity in the formation of tricarbonyliron complexes of **2**.

when the hydroxyl groups are derivatised as ethers or esters (**6** → **7**). It has previously been proposed [13] that such selectivity might be due to the incoming 16 valence-electron $Fe(CO)_4$ fragment coordinating to a hydroxyl oxygen in the first instance (**8**, Scheme 2b), before migration to form $[\eta^2]$ alkene complex **9**, loss of another carbonyl ligand and formation of **5**.

We have previously studied the organoiron [14] and organocobalt [15] chemistry of derivatives of *ipso*, *ortho* diol **4**. Since **4** possesses Lewis basic groups on both faces of the cyclohexadiene ring, formation of either diastereomer (diol *endo* or diol *exo*) could be envisaged. In the event, complexation of methyl ester **10** gave only complex **11** (diol *endo*), indicating that pre-coordination to the




**Scheme 3.** Facial selectivity in the formation of tricarbonyliron complexes of derivatives of **4** ("LA" = Lewis acid).

[17]. For dienyl ligands bearing terminal esters (such as **16**), a marked preference has been noted for addition of nucleophiles ω-to the ester, as opposed to *ipso* to the ester [18]. Additionally, nucleophiles generally add to $[\eta^5]^+$ dienyl ligands *exo* to the iron [19]. Therefore, recombination of the tethered nucleophile in **16** will give rise to $[\eta^4]$ complex **13**.

We subsequently sought deliberately to exploit $[\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4]$ transformations from complex **11** for the purposes of diversifying the cyclohexadiene ligand [14c]. Such reaction sequences have been reported previously for tricarbonyliron complexes derived from arene *cis*-diols of type **2** [12a–d,f,g]. In such complexes, the hydroxyl groups (or derivatives thereof) may be lost one of two ways. Treatment with Brønsted acid and C–O bond cleavage gives an $[\eta^5]^+$ complex, or alternatively, dehydroxylation/dealkoxylation with trityl salts can be used, although this latter method can suffer from competing hydride abstraction (leading to oxidation to a ketone). Once the $[\eta^5]^+$ complex has been formed, in the absence of an intramolecular nucleophile, the complexes may be isolated and characterised. Subsequent addition of a nucleophilic species then results in nucleophilic addition to give a new $[\eta^4]$ complex. Of course, when tricarbonyliron complexes formed from arene *cis*-diols are used, a regioselectivity issue may occur: since there are two hydroxyl groups, either of which might be lost, two regioisomeric $[\eta^5]^+$ complexes may arise. It has been determined that for complexes of types **5** or **7** (derived from *ortho*, *meta*-diols of type **2**), the nature of the substituent influences the regioselectivity in $[\eta^5]^+$ complex formation (for example, a highly electron-withdrawing trifluoromethyl substituent on the diene leads to highly selective extrusion of the distal hydroxyl group when forming the $[\eta^5]^+$ complex). However, for complex **11** (derived from *ipso*, *ortho*-diol **4**), the ester substituent is not conjugated to the diene, so low regioselectivity was anticipated.

In the event, upon treatment of **11** with $HBF_4$ in acetic anhydride, two cations **17** and **18** were indeed formed (**17**:**18** ≈ 1:4) [14c]. Acetic anhydride was used as solvent in order to effect *in situ*

*O*-acetylation [20], since $[\eta^5]^+$ cyclohexadienyl complexes with a free *endo* hydroxyl group at C6 are known to be unstable [13b]. When the resultant mixture of cations was then treated with various nucleophiles, the two regioisomeric $[\eta^4]$ complexes **19** and (±)-**20** were obtained, with (±)-**20** as the major product (Scheme 4). In the formation of **19** from **17**, complete selectivity for addition of a nucleophile ω-to an ester is once again observed. In the formation of (±)-**20**, racemic products were always obtained despite the fact that **11** is a single enantiomer. This is due to the fact that $[\eta^5]^+$ complex **18** possesses a plane of symmetry and is therefore achiral. The reaction sequence **11** → **18** → **20** is a *homochiral* $[\eta^4]$ → *achiral* $[\eta^5]^+$ → *racemic* $[\eta^4]$ process; comparable sequences for other tricarbonyliron cyclohexadiene complexes have been disclosed [21]. All of the products **19** and (±)-**20** smoothly underwent oxidative decomplexation of the tricarbonyliron fragment (except **20**, Nu = H), so giving a range of novel cyclohexadienes for use in synthesis.

Both **19** and (±)-**20** possess a residual acetoxy group, which could be induced to leave by treatment with Brønsted acid; this would lead to formation of another $[\eta^5]^+$ complex, which in turn could be treated with another nucleophile to give a further $[\eta^4]$ complex. By this approach, both hydroxyl groups of the original arene *cis*-diol could be substituted with any desired nucleophile. Overall, therefore, a highly versatile $[\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4]$ sequence could allow for rapid diversification of the initial tricarbonyliron complexes. One example of such a sequence employing an arene *cis*-diol starting material has been reported, namely Stephenson's approach to hippeastrine [22]. One motivation for wishing to employ such a sequence with a complex derived from *ipso*, *ortho*-diol **4** was to effect a formal synthesis of oseltamivir **27** (Tamiflu®). This anti-influenza medication has been the subject of a great many synthetic studies [23], including several that utilise arene *cis*-diol starting materials [24]. Additionally, one of us had already reported a total synthesis of (−)-oseltamivir that utilised tricarbonyliron methodology [18b]. A combination of this synthesis with an $[\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4]$ sequence from **4** allowed for a formal synthesis of (±)-oseltamivir, as shown in Scheme 5[14c].

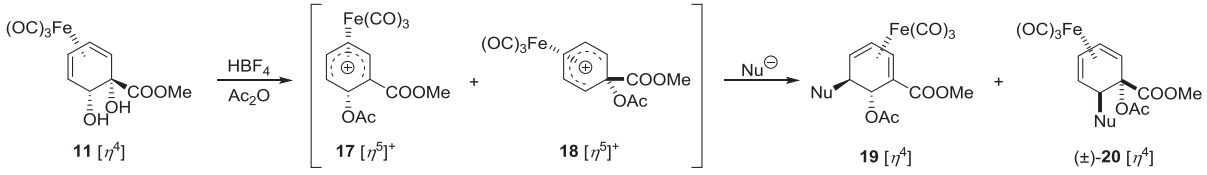
As oseltamivir possesses an ethyl ester side chain, the required $[\eta^4]$ complex **22** was prepared in analogous fashion to **11**. Treatment of **22** with Brønsted acid in acetic anhydride gave the expected regioisomeric mixture of $[\eta^5]^+$ complexes. Treatment of this mixture with sodium borohydride then gave isomeric $[\eta^4]$ **23** and (±)-**24**, each with a methylene unit in the ring. The major product was the desired complex (±)-**24**, which was treated with Brønsted acid once again (this time in dichloromethane) to effect loss of the second acetyl group and formation of the second $[\eta^5]^+$ complex in the sequence, (±)-**25**. Finally, treatment of (±)-**25** with the second nucleophile (*tert*-butylcarbamate) and base gave (±)-**26**, an intermediate previously reported in our 2007 synthesis of oseltamivir [18b].

The sequence depicted in Scheme 5 has the potential to allow for the introduction of substituents at C6, by use of a different nucleophile in the first $[\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4]$ sequence, instead of simply effecting a reductive "defunctionalisation" with borohydride. Although many analogues of oseltamivir have been prepared and evaluated, substitution at C6 has been comparatively underexplored. The original drug discovery programme which led to the development of oseltamivir also evaluated an analogue bearing a methyl group at C6, *anti* to the amine at C5 [25]. This substitution was found to be deleterious ($>10^3$ weaker binding to influenza A neuraminidase); a subsequent modelling study suggests this is due to undesirable steric interactions [26]. However, due to the aforementioned tendency for nucleophiles to add to tricarbonyliron $[\eta^5]^+$ dienyl complexes *exo* to the metal, our methodology would allow for the introduction of C6 substituents *syn* to the C5 amine, not *anti*. Indeed, more recent work from Pinto et al. has shown that a substituent at C6 *syn* to the C5 group is not only tolerated, but may impart particular benefits [27]. Specifically, a substituent with this configuration at C6 is able to interact with the so-called "150 cavity", a potential additional binding site located near the active site of neuraminidase [28]. On the basis of the above rationale, we sought to synthesise an analogue of oseltamivir with a substituent at C6; this paper describes our results in this regard.

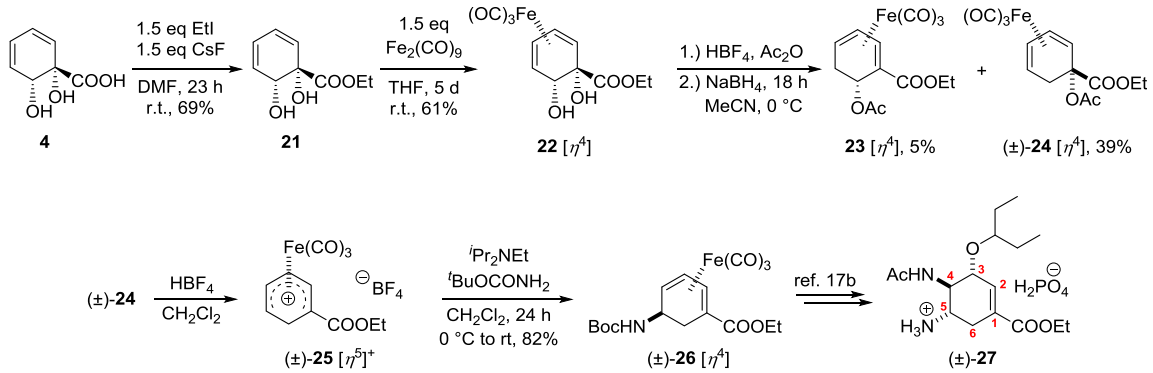
## 2. Results and discussion

Ethyl ester $[\eta^4]$ complex **22** was synthesised as previously described [14c]. Treatment of **22** with tetrafluoroboric acid—diethyl etherate in acetic anhydride led to formation of cations **28** and (achiral) **29**. NMR analysis of the reaction mixture indicated these to be present in the ratio **28**:**29** ≈ 1:14 (Scheme 6). Whereas in our previous work we had never attempted the separation or characterisation of **28** and **29**, in the current case we were able to develop a protocol to effect the removal of unwanted **28**. This exploited the seemingly lower solubility of **28** than **29**. Thus, dilution of the reaction mixture with diethyl ether led to formation of a precipitate. Filtration and analysis of the solid showed it to consist of a mixture of **28**:**29** ≈ 2:3, whereas concentration of the filtrate under reduced pressure gave pure **29**. The yield of pure **29** varied between 50% and 80% upon repetition of this procedure. The $[\eta^5]^+$ complex **29** was crystalline and an x-ray crystal structure was obtained (Fig. 1).

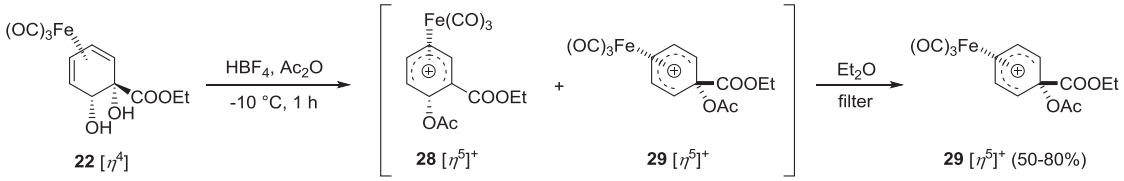
Inspection of the crystallographic data shows the $[\eta^5]$ dienyl fragment in **29** to be almost coplanar, as expected (with dihedral angles of $C^2–C^3–C^4–C^5 = 2.6(3)^\circ$ and $C^3–C^4–C^5–C^6 = 1.4(3)^\circ$; numbering as per Fig. 1). The "pucker" of the cyclohexadienyl ring is clearly visible, with $C^1$ more distant from the metal centre than the other ring carbons (and with dihedral angles of $C^1–C^2–C^3–C^4 = 24.9(3)^\circ$ and $C^1–C^6–C^5–C^4 = 27.3(3)^\circ$). The Fe–$C^1$ distance (i.e. between the $sp^3$-hybridised ring carbon and the metal centre) is 2.725(2) Å. To our knowledge, there is a single previous literature report of a crystal structure of a cationic tricarbonyliron(0) cyclohexadienyl complex where the $sp^3$ carbon is a quaternary carbon [29]. In this report, the Fe–$C^1$ distance is 2.670 Å. In contrast, some fourteen crystal structures have been reported for analogous complexes where the $sp^3$ carbon is *not* a quaternary carbon [30]. For these structures, the reported Fe–$C^1$ distances range from 2.456(4) Å to 2.733(9) Å. Therefore, the presence of the *endo* acetoxy group in **29** does not appear to distort significantly the




**Scheme 4.** Formation of $[\eta^5]^+$ complexes from **11** and their reaction with nucleophiles. Nu = $PhS^-$, $H^-$ (from $NaBH_4$), $N_3^-$, $HO^-$.




**Scheme 5.** Our previously reported formal synthesis of (±)-oseltamivir **27**.




**Scheme 6.** Synthesis of $[\eta^5]^+$ complexes **28** and **29**.

geometry of the cyclohexadienyl ligand. The bond lengths Fe–$C^3$, Fe–$C^4$ and Fe–$C^5$ are all equivalent within 3σ, whereas the bonds to the dienyl termini (Fe–$C^2$ and Fe–$C^6$) are longer. Inspection of the NMR data for **29** clearly illustrates its achiral nature, since for the dienyl ligand, only three proton resonances are observed (in a 1:2:2 ratio), indicative of the plane of symmetry in the molecule.

Having fully characterised **29**, we next examined the addition of a nucleophile other than hydride. We opted to use

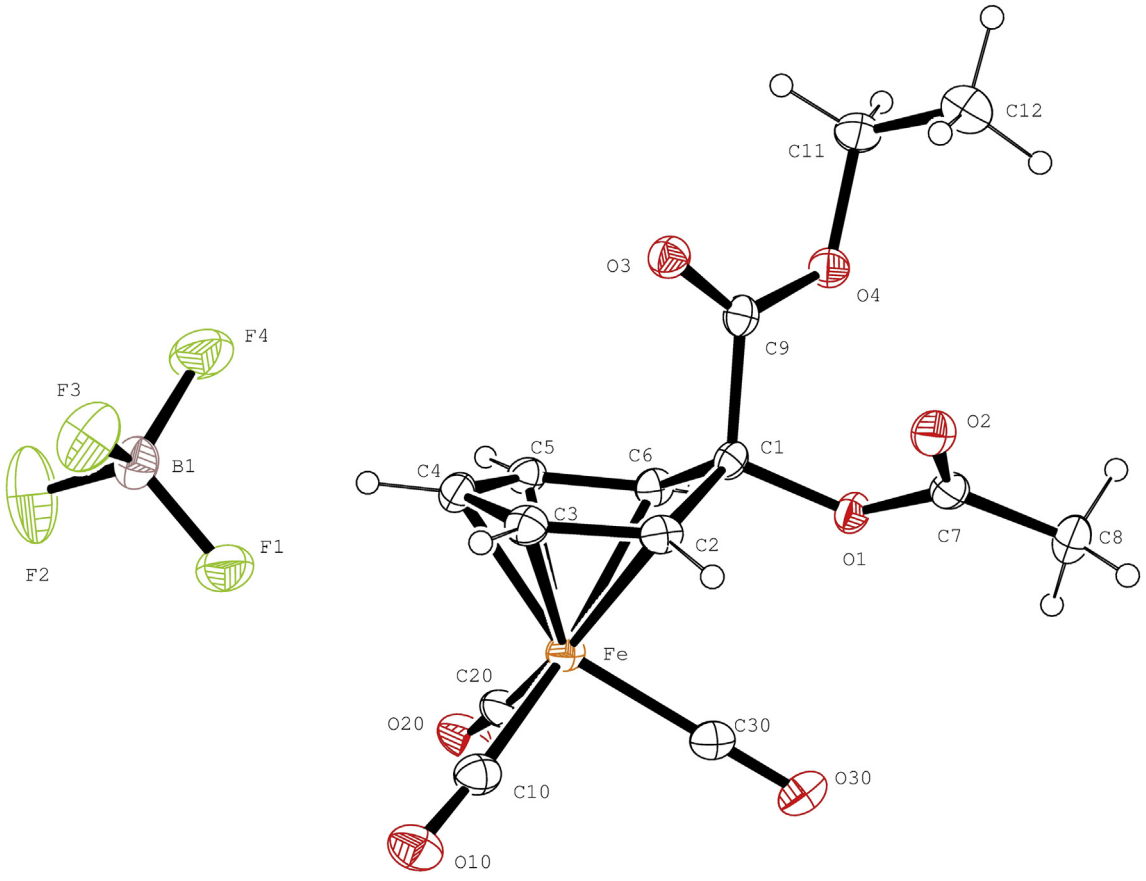
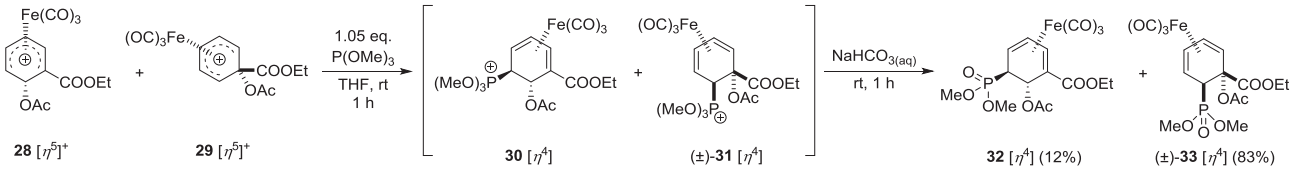



**Fig. 1.** Solid state structure of **29**. Ellipsoids are represented at 30% probability. H atoms are shown as spheres of arbitrary radius. CCDC #1405160. For tables of crystallographic data, see the supporting information.




**Scheme 7.** Synthesis of phosphonates.

trimethylphosphite, as this would lead to installation of a phosphonate at C6 and there is some precedent for use of such a functional group in oseltamivir analogue design [24f,31]. Phosphites are among the less commonly used nucleophiles for addition to $[\eta^5]^+$ cyclohexadienyl tricarbonyliron(0) complexes [18e,32], but are nevertheless synthetically useful, insofar as the adducts formed readily undergo a Michaelis–Arbuzov reaction [33] to provide the corresponding phosphonates [32a]. With a view to preparing both possible novel isomeric $[\eta^4]$ complexes, we exposed the crude mixture of $[\eta^5]^+$ complexes **28** and **29** to trimethylphosphine in THF, followed by addition of sodium bicarbonate (Scheme 7). As expected, the major product was the desired (±)-**33**, arising from intermediate (±)-**31**. A small amount of isomeric **32**, arising from **30**, was also isolated. Products **32** and (±)-**33** were separated and fully characterised; crystals of (±)-**33** suitable for x-ray diffraction were obtained and the crystal structure is shown in Fig. 2.

To our knowledge, the crystal structure of (±)-**33** constitutes the first crystal structure of an $[\eta^4]$ diene tricarbonyliron complex bearing a phosphonate at an adjacent carbon. In this structure, the Fe–$C^3$ and Fe–$C^4$ bonds are unambiguously shorter than the Fe–$C^2$ and Fe–$C^5$ bonds. The $[\eta^4]$ portion of the ligand is almost planar, with a $C^2$–$C^3$–$C^4$–$C^5$ dihedral angle of 1.9(4)°. In the $^1$H NMR spectrum of (±)-**33**, the diastereotopic nature of the phosphonate methyl groups is clearly visible, as they give rise to two discrete doublets, each exhibiting $^3J_{CP}$ coupling. Additionally, the proton at $C^6$ resonates as a doublet of doublets, with $^2J_{HP}$ = 24.5 Hz and $^3J_{HH}$ = 3.0 Hz. All proton and carbon resonances were unambiguously assigned on the basis of 2D NMR experiments (see Supplementary information), with the exception of the diastereotopic methyl groups and also the protons at $C^3$ and $C^4$ (whose resonances overlap).

With the desired phosphonate (±)-**33** in hand, we then sought to undertake the second $[\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4]$ sequence. Accordingly, (±)-**33** was treated with $HBF_4$ in ether, giving rise to $[\eta^5]^+$

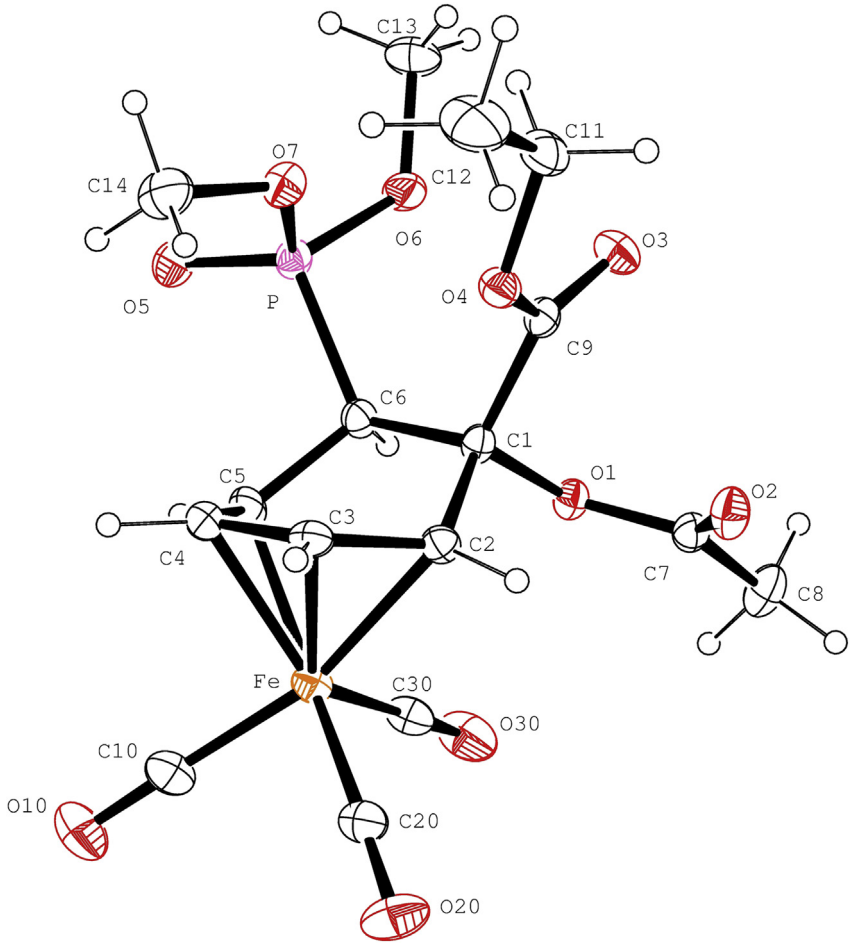


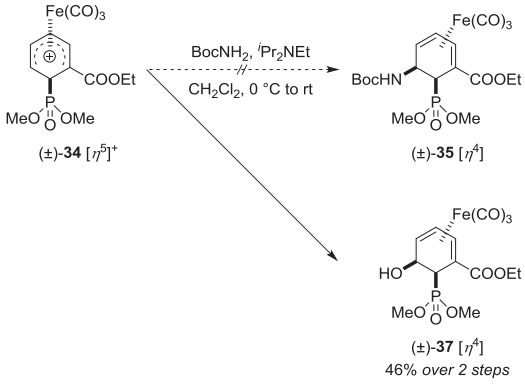

**Fig. 2.** Solid state structure of (±)-**33**. Ellipsoids are represented at 30% probability. H atoms are shown as spheres of arbitrary radius. CCDC #1405159. For tables of crystallographic data, see the supporting information.

cyclohexadienyl complex (±)-**34** (Scheme 8). Since only one leaving group remained in substrate (±)-**33**, there was no regiochemical ambiguity upon $[\eta^5]^+$ complex formation and (±)-**34** was the sole product. Unlike $[\eta^5]^+$ complex **29**, the $[\eta^5]^+$ complex (±)-**34** possesses no plane of symmetry, and the inequivalence of all positions on the cyclohexadienyl ligand is visible in the crude NMR spectra. It was our intention to effect the addition of *tert*-butylcarbamate to (±)-**34** in order to access (±)-**35**. As (±)-**35** is an analogue of (±)-**26** (Scheme 5), we planned to elaborate (±)-**35** to an analogue of oseltamivir, (±)-**36**, using the same methodology as was employed for converting (±)-**26** into (±)-oseltamivir **27**. However, when $[\eta^5]^+$ cyclohexadienyl complex (±)-**34** (used crude) was treated under the same conditions used to convert (±)-**25** to (±)-**26** (*i.e. tert*-butylcarbamate as nucleophile, Hünig's base, dichloromethane, 0 °C to room temperature, *c.f.* Scheme 5), we were surprised to find that (±)-**35** was not formed (Scheme 8).

After work-up, a new product was found to have been formed, but rather than the expected (±)-**35**, instead alcohol (±)-**37** was isolated in 46% overall yield from (±)-**33** (Scheme 9). This could be rationalised on the basis of $[\eta^5]^+$ complex (±)-**34** remaining inert towards the nitrogen nucleophile, yet reacting with water during the aqueous work-up. It has previously been reported that in cases where an $[\eta^5]^+$ complex has failed to react with a particular nucleophile, another type of byproduct may be isolated after aqueous workup, namely an ether arising from one molecule of water and two molecules of the $[\eta^5]^+$ complex [34]. We cannot rule out the formation of such an ether in the present case, as trace amounts of a material less polar than (±)-**37** were observed by TLC, but were not isolated. Crystals of novel $[\eta^4]$ complex (±)-**37** suitable for x-ray diffraction were obtained and the crystal structure of (±)-**37** is shown in Figs. 3 and 4.

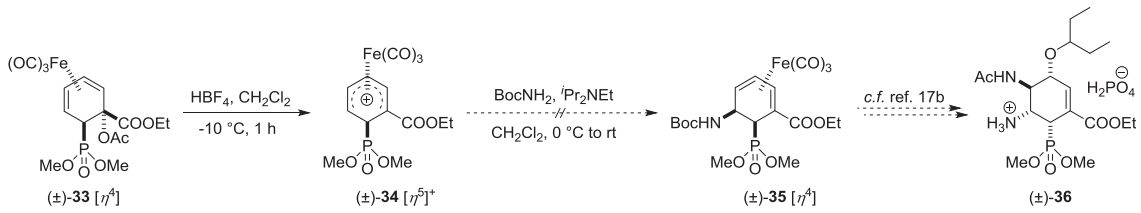
In the crystal structure of (±)-**37**, the Fe–$C^3$ and Fe–$C^4$ bonds are unambiguously shorter than the Fe–$C^2$ and Fe–$C^5$ bonds, as was the case for (±)-**33** also. However, in (±)-**37**, the Fe–$C^2$ bond is also unambiguously longer than the Fe–$C^5$ bond. This is possibly a consequence of the fact that in (±)-**37**, the ester group is conjugated to the diene (unlike in **29** and (±)-**33**), resulting in electronic perturbation of the $\eta^4$ ligand to some extent. Interestingly, a comparable lengthening is not observed in other reported crystal structures of $\eta^4$ cyclohexadiene tricarbonyliron(0) complexes bearing an ester on the diene terminus [14b,35]. The $\eta^4$ ligand in (±)-**37** also deviates slightly further from planarity than in (±)-**33**, with a $C^2$–$C^3$–$C^4$–$C^5$ dihedral angle of 3.3(2)°. The solid state structure of (±)-**37** shows intermolecular hydrogen bonding, with the hydroxyl hydrogen forming a bond to the P=O motif of an adjacent molecule (Fig. 4). In the $^1$H NMR spectrum of (±)-**37**, the inequivalence of the two diastereotopic phosphonate methyl groups is not as obvious as for (±)-**33**, due to a degree of peak broadening, but the inequivalence of the two diastereotopic protons of the ester methylene is clearly visible.

The failure of (±)-**34** to react with the *tert*-butylcarbamate nucleophile cannot be attributed to the nucleophile itself, as this has been shown previously to be capable of adding to $[\eta^5]^+$ dienyl tricarbonyliron(0) complexes as desired [14c,18b,36]. Rather, we attribute the lack of reaction to the nature of (±)-**34** itself. The phosphonate motif imparts steric bulk to (±)-**34** in comparison to (±)-**26**, and is located not only immediately adjacent to the desired site of nucleophilic addition, but also on the same face of the ligand the nucleophile would approach. As such it is plausible that the bulky phosphonate can retard attack of a nucleophile; this effect will be more significant when the nucleophile itself is sterically demanding (such as *tert*-butylcarbamate, but not water). The reaction outcome has some literature precedent; whereas $[\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4]$ sequences are often successful and high yielding for the homologous cycloheptadiene complexes [37], for cyclohexadiene complexes the final step in this sequence (i.e. addition of the second nucleophile to the $[\eta^5]^+$ complex already bearing an *exo* substituent in the 6-position) can often be more problematic.




**Scheme 9.** Serendipitous synthesis of (±)-**37**.

Whilst (±)-**37** was not the compound we sought, we nevertheless examined the decomplexation of the cyclohexadiene in this species, as the organic fragment (±)-**38** would be a novel and potentially synthetically useful substance in its own right. This decomplexation proved to be far from trivial, however, since the free cyclohexadiene (±)-**38** proved to be susceptible to dehydration/rearomatisation under many of the reaction conditions tried (Scheme 10). In the first instance, cerium ammonium nitrate-mediated decomplexation was attempted [38]. Unfortunately, the desired (±)-**38** was the minor product, and rearomatised **39** predominated. Use of an alternative oxidant to effect demetallation, trimethylamine-*N*-oxide [39], still gave mostly aromatised material. Finally, we employed basic hydrogen peroxide [40], noting that it had previously been employed to effect demetallation of a similar cyclohexadiene phosphonate complex (lacking a hydroxyl group) without incident [18e]. Gratifyingly, this reaction proved both to be exceedingly quick (5 min at 0 °C in EtOH) and also to provide (±)-**38** as the major product (45%) and **39** as the minor product (41%). In the $^1$H NMR spectrum of (±)-**38**, the $\beta$, $\gamma$ and $\delta$ protons of the




**Scheme 8.** Synthesis of the second cyclohexadienyl complex (±)-**34** and attempted synthesis of (±)-**35**.

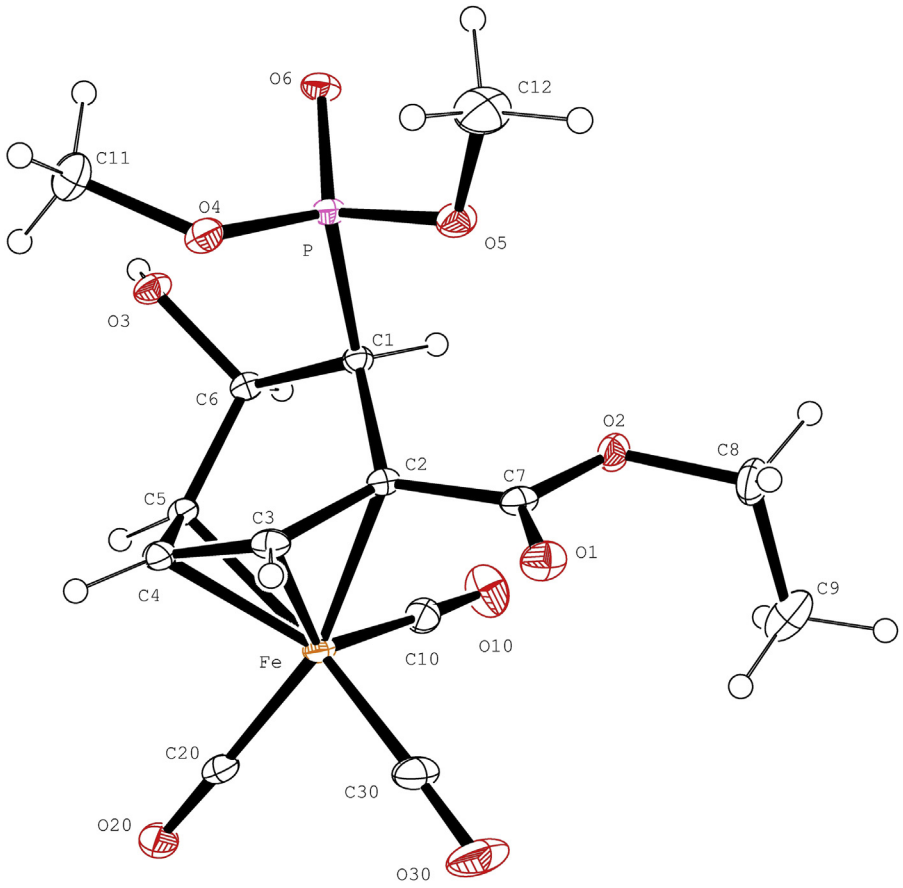



**Fig. 3.** Solid state structure of (±)-**37**. Ellipsoids are represented at 30% probability. H atoms are shown as spheres of arbitrary radius. CCDC #1408390. For tables of crystallographic data, see the supporting information.

uncomplexed α,β,γ,δ-unsaturated ester motif are clearly discernible. The two diastereotopic methyl groups give rise to two distinct resonances in the spectrum of (±)-**38**, whereas in the aromatic byproduct **39**, a single methyl environment is observed.

## 3. Conclusion

In conclusion, we have described a $[\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4]$ sequence for a tricarbonyliron(0) complex derived from **4**, a product of microbial arene oxidation. This sequence corresponds to (−)-**22** → **29** → (±)-**33** → (±)-**34** → (±)-**37**, and three of these five complexes have been characterised crystallographically. The final $[\eta^4]$ complex obtained, (±)-**37** was not that which was targeted. Trimethylphosphine and *tert*-butylcarbamate have previously both been shown to be competent nucleophiles for addition to tricarbonyl $[\eta^5]^+$ cyclohexadienyliron complexes in isolation. However, our current results suggest that their sequential use in a $[\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4]$ sequence to access a vicinal *syn* β-amino phosphonate is not viable. We ascribe the lack of formation of the desired (±)-**36** to steric hindrance of the approach of the bulky nucleophile *tert*-butylcarbamate to the appreciably congested electrophile (±)-**34**. Undesired product (±)-**37** was nevertheless treated with oxidant to disengage the $\eta^4$ ligand from the metal centre; the resultant cyclohexadiene (±)-**38** may find uses in synthesis in its own right, possessing as it does stereodefined and differentiated functionality for further elaboration. Further studies in our groups will evaluate the addition of other nucleophiles to (±)-**34**.

## 4. Experimental section

*General procedures*. Reactions were carried out under an atmosphere of nitrogen; all subsequent isolation and purification procedures were performed in a fumehood, open to the atmosphere. Solvents were dried and degassed by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to petroleum ether, bp 40–60 °C. TLCs were performed using aluminium-backed plates precoated with Alugram®SIL G/UV and visualized by UV light (254 nm) and/or $KMnO_4$ or cerium ammonium molybdate stains, followed by gentle warming. Flash column chromatography was carried out using Davisil LC 60 Å silica gel (35–70 micron) purchased from Fisher Scientifics. IR spectra were recorded on Perkin–Elmer 1600 FT IR spectrometer with absorbances quoted as ν in $cm^{-1}$. NMR spectra were run in $CDCl_3$ on Bruker Avance 300 or 400 MHz instruments at 298 K. Mass spectra were recorded with a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik). Specific rotations were recorded on an Optical Activity AA-10 Automatic polarimeter with a path length of 1 dm. Concentrations (c) are quoted in g/100 mL.

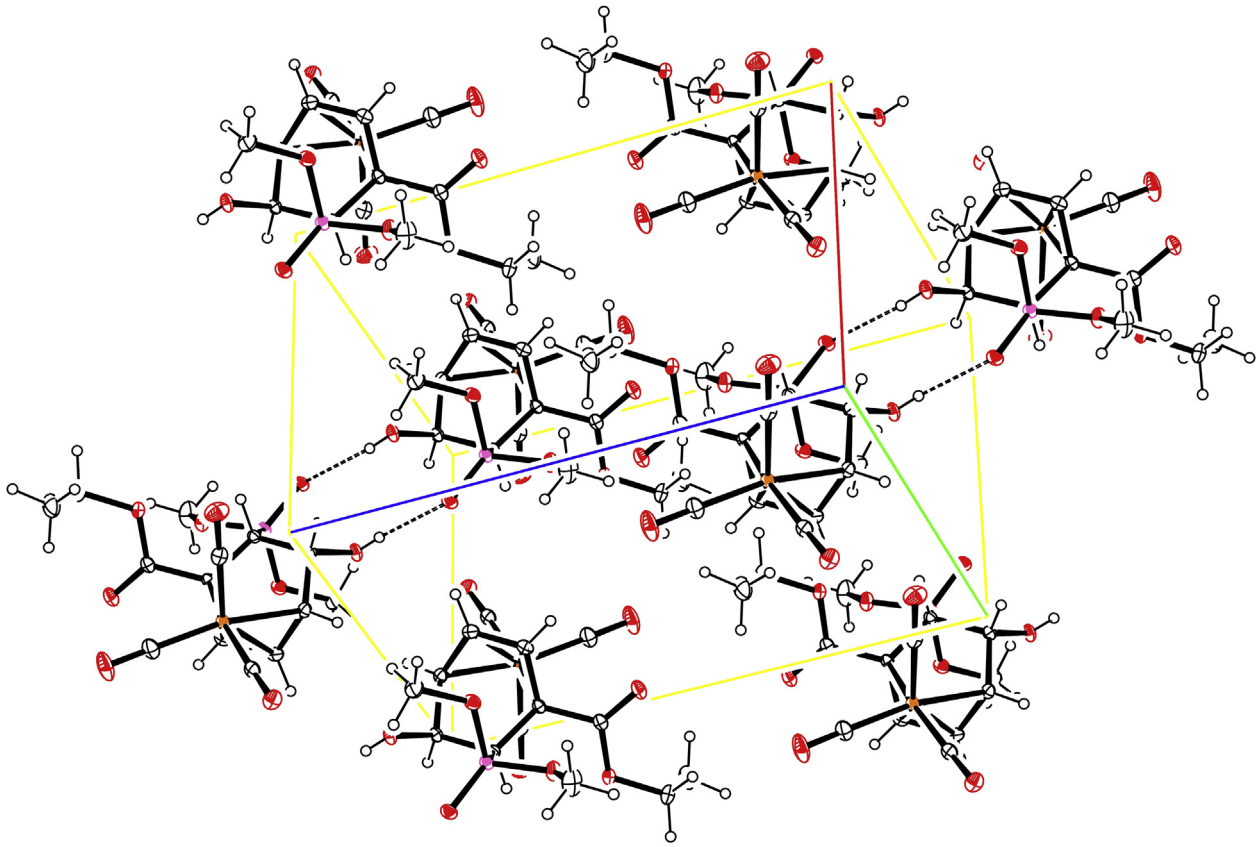
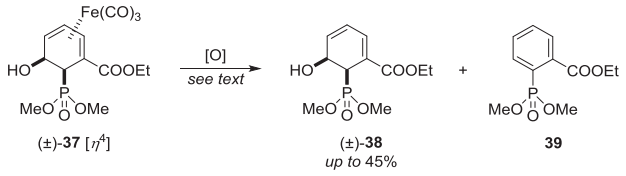


**Fig. 4.** Unit cell for (±)-**37**. Hydrogen bonds are shown as dashed lines.




**Scheme 10.** Demetallation of (±)-**37**.

*4.1. Tricarbonyl($\eta^5$-ethyl 6-(endo-acetyloxy)cyclohexadienyl-6-carboxylate)iron(+1) tetrafluoroborate(−1)* ***29****, (+)-(1S*)-Tricarbonyl($\eta^4$-(5R*,6R*)-ethyl 6-(acetyloxy)-5-(dimethoxyphosphoryl)cyclohexa-1,3-diene-1-carboxylate)iron(0) (+)-****32*** *and (±)-(1S*)-Tricarbonyl($\eta^4$-(5R*,6R*)-ethyl 5-(acetyloxy)-6-(dimethoxyphosphoryl)cyclohexa-1,3-diene-5-carboxylate) iron(0) (±)-****33***

To a solution of diol **22** (625 mg, 1.92 mmol, 1.00 equiv) in acetic anhydride (8.00 mL) was added tetrafluoroboric acid diethyl ether complex (1.05 mL, 7.71 mmol, 4.00 equiv) at −10 °C. The reaction mixture was stirred at −10 °C for 1 h, after which pre-cooled diethyl ether (60.0 mL) was added, resulting in the formation of pale yellow precipitate. The precipitate (shown by NMR to be a mixture of **28** and **29**) was filtered and the filtrate concentrated under reduced pressure and left standing for 16 h, allowing crystals of pure **29** to form. The crystals were washed with diethyl ether (3 × 5 mL), filtered, and dried. Crystals of **29** suitable for x-ray diffraction were grown. Both solids were then combined and the mixture of **28** and **29** was redissolved in THF (10.0 mL) followed by the addition of trimethylphosphine (238 μL, 2.02 mmol, 1.05 equiv) at rt. The reaction mixture was stirred at rt for 1 h resulting in a pale yellow to brown colour change. Saturated aqueous $NaHCO_3$ (15.0 mL) was added and the reaction mixture was left stirring for an additional 1 h at rt. The product was extracted using $CH_2Cl_2$ (3 × 30 mL), then combined organic phases were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, and purified by chromatography on silica gel (20% acetone in $Et_2O$) to give (+)-**32** (105 mg, 12%) and (±)-**33** (730 mg, 83%) as pale yellow gums. **29**: Pale yellow crystals; mp = 117–118 °C; $^1$H NMR (300 MHz, $CD_3CN$, numbering as per Fig. 1): δ = 6.90 (1H, tt, $J$ = 5.5, 1.0 Hz, $H^4$), 6.00 (2H, dd, $J$ = 7.0, 5.5 Hz, $H^3$, $H^5$), 4.19 (2H, dd, $J$ = 7.0, 1.0 Hz, $H^2$, $H^6$), 3.97 (2H, q, $J$ = 7.0 Hz, $H^{11}$), 2.18 (3H, s, $H^8$), 1.08 (3H, t, $J$ = 7.0 Hz, $H^{12}$); $^{13}$C NMR (75.4 MHz, $CD_3CN$): δ = 170.0 ($C^7$), 165.0 ($C^9$), 101.2 ($C^3$, $C^5$), 88.2 ($C^4$), 74.7 ($C^1$), 63.8 ($C^2$, $C^6$), 63.1 ($C^{11}$), 20.0 ($C^8$), 13.2 ($C^{12}$); FTIR (neat): $\nu_{max}$ = 2128, 2082, 1746, 1451, 1374, 1266, 1234, 1078, 952, 892, 854 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{14}H_{13}FeO_7$: 265.0158 $[M-(CO)_3]^+$; found: 265.0157. (+)-**32**: Pale yellow gum; $R_f$ = 0.33 (20:80 Acetone/$Et_2O$); $[\alpha]_D$ = +130 ($c$ = 0.1 in $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ = 6.04 (1H, br s, C$\underline{H}$=C–COOEt), 5.64 (1H, br s, =C$\underline{H}$–CH=C–COOEt), 5.39 (1H, br s, C$\underline{H}$-OAc), 4.22–4.02 (2H, m C$\underline{H}_2$CH$_3$), 3.78 (6H, br d, $J$ = 20.5 Hz, PO(OC$\underline{H}_3$)$_2$), 3.23 (1H, br s, C$\underline{H}$=CH–CH=C–COOEt), 2.49 (1H, br s C$\underline{H}$–PO(OCH$_3$)$_2$), 2.09 (3H, s OCOC$\underline{H}_3$), 1.23 (3H, t, $J$ = 7.0 Hz CH$_2$C$\underline{H}_3$); $^{13}$C NMR (75.4 MHz, $CDCl_3$): δ = 170.5 (O$\underline{C}$OCH$_3$), 169.0 (C$\underline{O}$OEt), 90.9, 83.6, 67.5 (d, $J$ = 23.0 Hz), 61.1 ($\underline{C}H_2CH_3$), 54.1, 53.8, 52.9, 21.1 ($\underline{C}OCH_3$), 13.9 ($CH_2\underline{C}H_3$) ppm; $^{31}$P NMR (121.5 MHz, $CDCl_3$): δ = 28.9 ppm; FTIR (neat): $\nu_{max}$ = 2951, 2854, 2052, 1968, 1740, 1448, 1368, 1248, 1214, 1026, 959, 793, 677 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{16}H_{19}FeO_{10}P$: 480.9957 $[M+Na]^+$; found: 481.0053. (±)-**33**: Pale yellow crystals; mp = 107 °C; $R_f$ = 0.47 (20:80 Acetone/$Et_2O$); $^1$H NMR (400 MHz, $CDCl_3$; numbering as per Fig. 2): δ = 5.54–5.47 (2H, m, $H^3$ and $H^4$),

4.09 (2H, q, $J$ = 7.0 Hz, $H^{11}$), 3.75 (1H, d, $J$ = 6.0 Hz, $H^2$), 3.67 (3H, d, $^3J_{HP}$ = 5.5 Hz, $H^{13}$ or $H^{14}$), 3.64 (3H, d, $^3J_{HP}$ = 5.5 Hz, $H^{13}$ or $H^{14}$), 3.14 (1H, br s, $H^5$), 2.63 (1H, dd, $^2J_{HP}$ = 24.5 Hz, $^3J_{HH}$ = 3.0 Hz, $H^6$), 2.08 (3H, s, $H^8$), 1.22 (3H, t, $J$ = 7.0 Hz, $H^{12}$);$^{13}$C NMR (75.4 MHz, $CDCl_3$; numbering as per Fig. 2): δ = 209.7 ($C^{10}$/$C^{20}$/$C^{30}$), 169.7 ($C^7$), 168.0 (d, $^3J_{CP}$ = 4.0 Hz, $C^9$), 85.7 ($C^3$), 85.3 (d, $^3J_{CP}$ = 4.0 Hz, $C^4$), 84.1 (d, $^2J_{CP}$ = 9.5 Hz, $C^1$), 62.3 ($C^{11}$), 61.6 (d, $^3J_{CP}$ = 11.0 Hz, $C^2$), 54.2 (d, $^2J_{CP}$ = 9.0 Hz, $C^5$), 53.0 (d, $^2J_{CP}$ = 10.5 Hz, $C^{13}$ or $C^{14}$), 52.9 (d, $^2J_{CP}$ = 10.5 Hz, $C^{13}$ or $C^{14}$), 47.9 (d, $^1J_{CP}$ = 132.0 Hz; $C^6$), 21.2 ($C^8$), 13.6 ($C^{12}$) ppm; $^{31}$P NMR (121.5 MHz, $CDCl_3$): δ = 24.9 ppm; FTIR (neat): $\nu_{max}$ = 2951, 2854, 2052, 1968, 1740, 1448, 1368, 1248, 1214, 1026, 959, 793, 677 $cm^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{16}H_{19}FeO_{10}P$: 459.0143 $[M+H]^+$; found: 459.0148; $m/z$ calcd for $C_{16}H_{19}FeO_{10}P$: 480.9957 $[M+Na]^+$; found: 480.9933.

### 4.2. (±)-(1R*)-Tricarbonyl(η$^5$-(6S*)-ethyl 6-(dimethoxyphosphoryl) cyclohexadienyl-1-carboxylate)iron(+1) tetrafluoroborate(−1) (±)-**34**

To a solution of phosphonate (±)-**33** (126 mg, 0.275 mmol, 1.00 equiv) in dichloromethane (5.00 mL) was added tetrafluoroboric acid diethyl ether complex (45 μL, 0.330 mmol, 1.20 equiv) at −10 °C. The reaction mixture was stirred at −10 °C for 1 h, after which pre-cooled diethyl ether (10.0 mL) was added, resulting in the formation of pale yellow precipitate. The precipitate was filtered and washed with further diethyl ether (3 × 10 mL), then dried in air to give (±)-**34** (crude product was used without purification) as a pale yellow gum; $^1$H NMR (300 MHz, CDCN): δ = 7.35 (1H, br s, η-C$\underline{H}$–CH–C–COOEt), 6.63 (1H, br s, η-C$\underline{H}$–C-COOEt), 5.99 (1H, br s, η-C$\underline{H}$–CH–CH–C–COOEt), 4.63 (1H, app q, $J$ = 7.0 Hz, η-C$\underline{H}$–CH–CH–CH–C–COOEt), 4.27 (2H, br d, $J$ = 6.0 Hz, C$\underline{H_2}$CH$_3$), 3.58 (6H, br s, PO(OC$\underline{H_3}$)$_2$), 1.25 (3H, t, $J$ = 6.5 Hz, CH$_2$C$\underline{H_3}$); the resonance for C$\underline{H}$–P was not observed; $^{13}$C NMR (75.4 MHz, CDCN): δ = 166.1 (COOEt), 103.7, 102.4, 91.4, 83.5 (visible in HSQC), 64.1 (C$\underline{H_2}$CH$_3$), 54.8 (PO(OC$\underline{H_3}$)$_2$), 13.6 (CH$_2$C$\underline{H_3}$); two resonances were not observed; $^{31}$P NMR (121.5 MHz, CDCN): δ = 16.6 ppm; FTIR (neat): $\nu_{max}$ = 2960, 2927, 2860, 2131, 2087, 1725, 1462, 1379, 1273, 1122, 1072, 1040, 962, 855, 778, 743, 705 $cm^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{14}H_{16}FeO_8P^+$: 398.9927 $[M]^+$; found: 398.9974.

### 4.3. (±)-(1R*)-Tricarbonyl(η$^4$-(5R*,6S*)-ethyl 6-(dimethoxyphosphoryl)-5-hydroxycyclohexa-1,3-diene-1-carboxylate)iron(0) (±)-**37**

To a suspension of (±)-**34** prepared as described above (assumed to be 0.275 mmol, 1.000 equiv) and *tert*-butylcarbamate (48.0 mg, 0.413 mmol, 1.50 equiv) in dichloromethane (3.00 mL) at 0 °C was added dropwise di*iso*propylethylamine (72.0 μL, 0.413 mmol, 1.50 equiv). The reaction mixture was stirred at 0 °C for 15 min, after which it was allowed to warm to rt over 2 h whilst stirring. The reaction mixture was diluted with dichloromethane (10.0 mL) and washed with 10% w/v aqueous citric acid solution (3 × 10 mL). The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by chromatography on silica (20% acetone in $Et_2O$) to give (±)-**37** (53 mg, 46% from (±)-**33**) as a pale yellow gum; $R_f$ = 0.30 (20:80 Acetone/$Et_2O$); $^1$H NMR (300 MHz, $CDCl_3$, Numbering as per Fig. 3): δ = 6.24 (1H, br s, $H^3$), 5.42 (1H, br s, $H^4$), 4.65 (1H, br s, $H^6$), 4.27–4.19 (1H, m, $H^8$), 4.13–4.05 (1H, m, $H^8$), 3.81–3.68 (7H, m, $H^1$, $H^{11}$, $H^{12}$), 3.40–3.30 (2H, m, $H^5$, OH), 1.27 (3H, t, 7.0 Hz, $H^9$); $^{13}$C NMR (75.4 MHz, $CDCl_3$, Numbering as per Fig. 3): δ = 210.9 ($C^{10}$/$C^{20}$/$C^{30}$), 170.7 ($C^7$), 86.4 ($C^3$), 85.8 ($C^4$), 71.4 ($C^6$), 64.0 ($C^5$), 60.8 ($C^8$), 55.8 (br, $C^2$), 53.1 (br, $C^{11}$ or $C^{12}$), 53.0 (br, $C^{11}$ or $C^{12}$),14.2 ($C^9$) (the resonance for $C^1$ was not observed); $^{31}$P NMR (121.5 MHz, $CDCl_3$): δ = 29.2 ppm; FTIR (neat): $\nu_{max}$ = 3327, 2956, 2058, 1985, 1709, 1449, 1276, 1213, 1066, 1033, 824, 792, 666, 610 $cm^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{14}H_{17}FeO_9P$: 438.9852 $[M+Na]^+$; found: 438.9875.

### 4.4. Ethyl (5S*,6R*)-6-(dimethoxyphosphoryl)-5-hydroxycyclohexa-1,3-diene-1-carboxylate (±)-**38** and Ethyl 2-(dimethoxyphosphoryl)benzoate **39**

To a solution of (±)-**37** (23 mg, 0.045 mmol, 1.0 equiv) in ethanol (1.5 mL) at 0 °C was added 35% aqueous hydrogen peroxide (310 μL, 3.53 mmol, 79.0 equiv), followed by the dropwise addition of 1 M NaOH (270 μL, 0.27 mmol, 6.0 equiv). The reaction mixture was stirred for 5 min at 0 °C, after which 1.0 M aqueous sodium thiosulfate (10 mL) was added and the product was extracted using dichloromethane (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by chromatography on silica (20% acetone in $Et_2O$) to give (±)-**38** (5.6 mg, 45%) and **39** (4.8 mg, 41%). (±)-**38**: colourless gum; $R_f$ = 0.24 (20:80 Acetone/$Et_2O$); $^1$H NMR (500 MHz, $CDCl_3$, numbering as per Fig. 3): δ = 7.08 (1H, t, $J$ = 5.8 Hz, $H^5$), 6.22 (1H, d, $J$ = 10.6 Hz, $H^3$), 6.05–6.02 (1H, m, $H^4$), 4.95 (1H, dd, $^2J_{HP}$ = 55.5 Hz, $^3J_{HH}$ = 8.0 Hz, $H^1$) 4.31–4.20 (2H, m, $H^8$), 3.81 (1H, d, $J$ = 11.3 Hz, OH), 3.77 (3H, d, $^3J_{HP}$ = 11.0 Hz, $H^{11}$ or $H^{12}$), 3.70 (3H, d, $^3J_{HP}$ = 11.0 Hz, $H^{11}$ or $H^{12}$), 3.64 (1H, dd, $^3J_{HP}$ = 21.5 Hz, $^3J_{HH}$ = 8.8 Hz, $H^6$), 1.32 ppm (3H, t, $J$ = 7.1 Hz, $H^9$); $^{13}$C NMR (125.76 MHz, $CDCl_3$, numbering as per Fig. 3): δ = 165.4 ($C^7$), 141.0 (d, $^3J_{CP}$ = 7.6 Hz, $C^3$), 134.7 (d, $^3J_{CP}$ = 10.2 Hz, $C^5$), 125.8 (d, $^2J_{CP}$ = 12.6 Hz; $C^2$), 123.4 ($C^4$), 69.1 (d, $J_{CP}$ = 9.0 Hz, $C^6$), 61.1 ($C^8$), 53.5 (d, $^2J_{CP}$ = 6.6 Hz, $C^{11}$ or $C^{12}$), 52.6 (d, $^2J_{CP}$ = 6.3 Hz, $C^{11}$ or $C^{12}$), 14.2 ($C^9$) ppm (the resonance for $C^1$ was not observed); $^{31}$P NMR (121.5 MHz, $CDCl_3$): δ = 29.5 ppm; FTIR (neat): $\nu_{max}$ = 3339, 2960, 1709, 1274, 1216, 1030, 1062, 826, 768, 626 $cm^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{11}H_{17}O_6P$: 299.0655 $[M+Na]^+$; found: 299.0677. **39**: pale yellow gum; $R_f$ = 0.61 (20:80 Acetone/$Et_2O$); $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.01–7.94 (1H, m, Ar–H), 7.79–7.74 (1H, m, Ar–H), 7.64–7.54 (2H, m, Ar–H), 4.41 (2H, q, $J$ = 7.0 Hz, C$\underline{H_2}$CH$_3$), 3.81 (6H, d, $^3J_{HP}$ = 11.5 Hz, PO(OC$\underline{H_3}$)$_2$), 1.41 (3H, t, $J$ = 7.0 Hz, CH$_2$C$\underline{H_3}$); HRMS (ESI): $m/z$ calcd for $C_{11}H_{15}O_5P$: 281.0549 $[M+Na]^+$; found: 281.0613.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.organchem.2015.09.005.

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