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.

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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 $[\eta^5]$ 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 $[\eta^5]$ 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 $\rightarrow$ 5) and also...
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)₅ fragment coordinating to a hydroxyl oxygen in the first instance (8, Scheme 2b), before migration to form [η⁶⁺] 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 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 [η⁶⁺] → [η⁶⁺⁺] → [η⁶⁺] sequence [16]. Thus, the initially formed [η⁶⁺] complex 14 coordinates an unidentified Lewis acidic species to give [η⁶⁺] complex 15, in which the acetonide oxygen has been rendered cationic (and hence a good leaving group). Extrusion of this leaving group gives [η⁶⁺⁺⁺] complex 16, which bears a tethered nucleophile. Such [η⁶⁺⁺⁺] cyclohexadienyl complexes are known readily to undergo addition of nucleophiles at the termini of the dienyl ligand [17]. For dienyl ligands bearing terminal esters (such as 16), a marked preference has been noted for addition of nucleophiles α-to the ester, as opposed to ipso to the ester [18]. Additionally, nucleophiles generally add to [η⁶⁺⁺] dienyl ligands exo to the iron [19]. Therefore, recombination of the tethered nucleophile in 16 will give rise to [η⁶⁺] complex 13.

We subsequently sought deliberately to exploit [η⁶⁺] → [η⁶⁺⁺] → [η⁶⁺] transformations from complex 11 for the purposes of diversifying the cyclohexadiene ligand [14c]. Such re-action 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 [η⁶⁺⁺] 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 [η⁶⁺⁺⁺] 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 [η⁶⁺] 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 [η⁶⁺⁺⁺] 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 [η⁶⁺⁺⁺] 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 [η⁶⁺⁺⁺⁺] 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 HBF₄ 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 $(\pm)$-20 were obtained, with $(\pm)$-20 as the major product (Scheme 4).

In the formation of 19 from 17, complete selectivity for addition of a nucleophile $\omega$-to an ester is once again observed. In the formation of $(\pm)$-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 $11 \rightarrow 18 \rightarrow 20$ is a homochiral $[\eta^5]$→ achiral $[\eta^5]$→ racemic $[\eta^4]$ process; comparable sequences for other tricarbonyliron cyclohexadiene complexes have been disclosed [21]. All of the products 19 and $(\pm)$-20 smoothly undergo oxidative decomplexation of the tricarbonyliron fragment (except 20, $\text{Nu} = \text{H}$), so giving a range of novel cyclohexadienes for use in synthesis.

Both 19 and $(\pm)$-20 possess a residual acetoxo group, which could be induced to leave by treatment with Brønsted acid; this would lead to formation of another $[\eta^4]$ 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 $[\eta^4]$→ $[\eta^3]$→ $[\eta^2]$→ $[\eta^1]$→ $[\eta^0]$ 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 oseltamivir, as shown in Scheme 5 [14c].

As oseltamivir possesses an ethyl ester side chain, the required $[\eta^4]$ complex 22 was synthesised as previously described [14c]. Treatment of 22 with tetrafluoroboric acid–diethyl ether 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 $28:29 \approx 1:1$ (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 $28:29 \approx 2:3$, 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 $C^1-C^2-C^3-C^4 = 2.6(3)^\circ$ and $C^1-C^4-C^5-C^6 = 1.4(3)^\circ$; 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 $C^1-C^4-C^5-C^6 = 27.3(3)^\circ$). The Fe–C1 distance (i.e. between the sp3–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 sp3 carbon is a quaternary carbon [29]. In this report, the Fe–C1 distance is 2.670 Å. In contrast, some fourteen crystal structures have been reported for analogous complexes where the sp3 carbon is not a quaternary carbon [30]. For these structures, the reported Fe–C1 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

\begin{center}
\textbf{Scheme 4.} Formation of $[\eta^5]^+$ complexes from 11 and their reaction with nucleophiles. \text{Nu} = \text{PhS}^-, \text{H}^+ (\text{from NaBH}_4), \text{Ni}, \text{HO}^-.
\end{center}
geometry of the cyclohexadienyl ligand. The bond lengths Fe–C\textsuperscript{3}, Fe–C\textsuperscript{4} and Fe–C\textsuperscript{5} are all equivalent within 3\(\sigma\), whereas the bonds to the dienyl termini (Fe–C\textsuperscript{2} and Fe–C\textsuperscript{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

![Scheme 5. Our previously reported formal synthesis of (±)-oseltamivir 27.](image)

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

![Scheme 6. Synthesis of [\(\eta^1\)]\(^+\) complexes 28 and 29.](image)


![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.](image)
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 \([\eta^5] \) 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 \((\pm) - 33\), arising from intermediate \((\pm) - 31\). A small amount of isomeric 32, arising from 30, was also isolated. Products 32 and \((\pm) - 33\) were separated and fully characterised; crystals of \((\pm) - 33\) suitable for x-ray diffraction were obtained and the crystal structure is shown in Fig. 2.

To our knowledge, the crystal structure of \((\pm) - 33\) constitutes the first crystal structure of an \([\eta^4] \) diene tricarbonyliron complex bearing a phosphonate at an adjacent carbon. In this structure, the Fe–C3 and Fe–C4 bonds are unambiguously shorter than the Fe–C2 and Fe–C5 bonds. The \([\eta^4] \) portion of the ligand is almost planar, with a C2–C3–C4–C5 dihedral angle of 1.9(4)°. In the 1H NMR spectrum of \((\pm) - 33\), the diastereotopic nature of the phosphonate methyl groups is clearly visible, as they give rise to two discrete doublets, each exhibiting \( J_{CP} \) coupling. Additionally, the proton at C6 resonates as a doublet of doublets, with \( J_{HP} = 24.5 \text{ Hz} \) and \( J_{HH} = 3.0 \text{ Hz} \).

With the desired phosphonate \((\pm) - 33\) in hand, we then sought to undertake the second \([\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4] \) sequence. Accordingly, \((\pm) - 33\) was treated with HBF\(_4\) in ether, giving rise to \([\eta^5]^+ \).
cyclohexadienyl complex (±)-34 (Scheme 8). Since only one leaving group remained in substrate (±)-33, there was no regiochemical ambiguity upon [η5]+ complex formation and (±)-34 was the sole product. Unlike [η5]+ complex 29, the [η6]+ 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 [η6]+ 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 6).

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 [η5]+ 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 [η5]+ complex has failed to react with a particular nucleophile, another type of byproduct may be isolated after aqueous work-up, namely an ether arising from one molecule of water and two molecules of the [η5]+ 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 [η5]+ 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–C3 and Fe–C4 bonds are unambiguously shorter than the Fe–C2 and Fe–C5 bonds, as was the case for (±)-33 also. However, in (±)-37, the Fe–C2 bond is also unambiguously longer than the Fe–C5 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 η5 ligand to some extent. Interestingly, a comparable lengthening is not observed in other reported crystal structures of η5 cyclohexadiene tricarbonyliron(0) complexes bearing an ester on the diene terminus [14b,35]. The η5 ligand in (±)-37 also deviates slightly further from planarity than in (±)-33, with a C3–C4–C5–C6 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 1H NMR spectrum of (±)-37, the inequivalence of the two diastereotropic phosphonate methyl groups is not as obvious as for (±)-33, due to a degree of peak broadening, but the inequivalence of the two diastereotropic 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 [η5]+ 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 sterico 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 [η4]+ → [η5]+ → [η6]+ → [η7]+ → [η8]+ 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 [η5]+ complex already bearing an exo substituent in the 6-position) can often be more problematic.

Whilst (±)-37 was not the compound we sought, we nevertheless examined the decomposition 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 decomposition 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 decomposition was attempted [38]. Unfortunately, the desired (±)-38 was the minor product, and re aromatised 39 pre-dominant. 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 1H NMR spectrum of (±)-38, the β, γ and δ protons of the
uncomplexed $\alpha\beta\gamma\delta$-unsaturated ester motif are clearly discernible. The two diastereotopic methyl groups give rise to two distinct resonances in the spectrum of $(\pm)$-38, whereas in the aromatic byproduct 39, a single methyl environment is observed.

3. Conclusion

In conclusion, we have described a \( [\eta^4] \rightarrow [\eta^3]^+ \rightarrow [\eta^1] \rightarrow [\eta^1] \) sequence for a tricarbonyliron(0) complex derived from 4, a product of microbial arene oxidation. This sequence corresponds to $(\pm)$-22 $\rightarrow$ 29 $\rightarrow$ $(\pm)$-33 $\rightarrow$ $(\pm)$-34 $\rightarrow$ $(\pm)$-37, and three of these five complexes have been characterised crystallographically. The final [\( \eta^1 \)] complex obtained, $(\pm)$-37 was not that which was targeted. Trimethylphosphine and tert-butylcarbamate have previously both been shown to be competent nucleophiles for addition to tricarbonyl $[\eta^3]^+$ cyclohexadienyliron complexes in isolation. However, our current results suggest that their sequential use in a $[\eta^1]^+ \rightarrow [\eta^1]^+ \rightarrow [\eta^1]^+ \rightarrow [\eta^1]^+$ sequence to access a vicinal $\alpha\beta$-amino phosphonate is not viable. We ascribe the lack of formation of the desired $(\pm)$-36 to steric hindrance of the approach of the bulky nucleophile tert-butylcarbamate to the appreciably congested electrophile $(\pm)$-34. Undesired product $(\pm)$-37 was nevertheless treated with oxidant to disengage the $\eta^1$ ligand from the metal centre; the resultant cyclohexadiene $(\pm)$-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 $(\pm)$-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 KMnO4 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 $\nu$ in cm$^{-1}$. NMR spectra were run in CDCl3 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. 3. Solid state structure of $(\pm)$-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.
4.1. Tricarbonyl(η²-ethyl 6-(endo-acetoxy)cyclohexadienyl-6-carboxylate)iron(+I) tetrafluoroborate(-I) 29, (+)-(1S*)-Tricarbonyl(η²-(5R*,6R*)-ethyl 6-(acetoxy)-5-(dimethoxyphosphoryl)cyclohexa-1,3-diene-1-carboxylate)iron(0) (-)-32 and (+)-(1S*)-Tricarbonyl(η²-(5R*,6R*)-ethyl 5-(acetoxy)-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, 1.05 equiv) at rt. The reaction mixture was stirred at 10 °C for 1 h, after which the mixture was cooled to 0 °C and filtered. Saturated aqueous NaHCO3 (15.0 mL) was added and the reaction mixture was left stirring for an additional 1 h at rt. The product was extracted using CH2Cl2 (3 × 30 mL), then combined organic phases were dried over MgSO4 and filtered. The filtrate was concentrated under reduced pressure, and purified by chromatography on silica gel (20% acetone in Et2O) to give (+)-32 (105 mg, 12%) and (±)-33 (730 mg, 83%) as pale yellow gums. Fig. 4. Unit cell for (±)-37. Hydrogen bonds are shown as dashed lines.

![Scheme 10. Demetallation of (±)-37.](image)

480.9957 [M+Na]+; found: 481.0053. (±)-33: Pale yellow crystals; mp = 117–118 °C; 1H NMR (300 MHz, CD3CN, numbering as per Fig. 1): δ = 6.90 (1H, t, J = 5.5, 1.0 Hz, H6), 6.00 (2H, dd, J = 7.0, 5.5 Hz, H5, H4), 4.19 (2H, dd, J = 7.0, 1.0 Hz, H2, H3), 3.97 (2H, q, J = 7.0 Hz, H11), 2.18 (3H, s, H8), 1.08 (3H, t, J = 7.0 Hz, H12); 13C NMR (75.4 MHz, CD3CN): δ = 170.0 (C2), 165.0 (C6), 101.2 (C3, C10), 88.2 (C5), 74.7 (C4), 63.8 (C2, C6), 63.1 (C11), 20.0 (C8), 13.2 (C12); FTIR (neat): νmax = 2128, 2082, 1746, 1451, 1374, 1266, 1234, 1078, 952, 892, 854 cm⁻¹; HRMS (ESI): m/z calcd for C14H13FeO7: 295.0148, found: 295.0157. (±)-32: Pale yellow gum; Rf = 0.33 (20:80 Acetone/ Et2O); [x]D = +130 (c = 0.1 in CHCl3); 1H NMR (300 MHz, CDCl3): δ = 6.04 (1H, br s, CH=CH–COOEt), 5.64 (1H, br s, =CH–CH=CH–COOEt), 5.39 (1H, br s, CH=CH–COOEt), 4.22–4.02 (2H, m CH2CH2), 3.78 (6H, br d, J = 20.5 Hz, PO(OCH3)2), 2.33 (1H, br s, =CH–CH=CH–COOEt), 2.49 (1H, br s, =CH–CH=CH–COOEt), 2.09 (3H, s OCOCH3), 1.23 (3H, t, J = 7.0 Hz, CH2CH3), 1.17 (3H, s, 3H, s OCOCH3), 1.17 (3H, s, 3H, s OCOCH3); 31P NMR (121.5 MHz, CDCl3): δ = 55.4–54.7 (2H, m, H3 and H4).
To a suspension 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 0 °C. The reaction mixture was stirred at 0 °C for 10 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; 1H NMR (300 MHz, CDCl3): δ = 7.35 (1H, br s, C–H), 6.63 (1H, br s, C–H), 5.99 (1H, br s, C–H), 4.63 (1H, app q, 7.0 Hz), 4.27 (2H, br d, J = 6.0 Hz, CH2CH2), 3.58 (6H, br s, PO(CH3)2), 1.25 (3H, t, 7.3 Hz, CH3CH2); the resonance for CH–P was not observed; 13C NMR (75.4 MHz, CDCl3): δ = 166.1 (COOEt), 103.7, 102.4, 91.4, 83.5 (visible in HSO4C), 64.1 (CH2CH2), 54.8 (PO(CH3)2), 13.6 (CH3CH2); two resonances were not observed; 31P NMR (121.5 MHz, CDCl3): δ = 16.66 ppm; FTIR (neat): νmax = 2960, 2927, 2860, 2131, 1807, 1725, 1462, 1379, 1273, 1122, 1072, 1040, 962, 855, 778, 743, 705 cm⁻¹; HRMS (ESI): m/z calc for C16H18FeO3P: 398.9972 [M + Na]^+; found: 398.9974.

4.3. (±)-(1'R)-Tricarbonyl(n^5-(SR,6S)-ethyl 6-(dimethoxyphosphoryl)-5-hydroxy-cyclohexa-1,3-diene-1-carboxylate)iron(–I) tetrafluoroborate(–I) (±)-37

To a suspension 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 0 °C. The reaction mixture was stirred at 0 °C for 10 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; 1H NMR (300 MHz, CDCl3): δ = 7.35 (1H, br s, C–H), 6.63 (1H, br s, C–H), 5.99 (1H, br s, C–H), 4.63 (1H, app q, 7.0 Hz), 4.27 (2H, br d, J = 6.0 Hz, CH2CH2), 3.58 (6H, br s, PO(CH3)2), 1.25 (3H, t, 7.3 Hz, CH3CH2); the resonance for CH–P was not observed; 13C NMR (75.4 MHz, CDCl3): δ = 166.1 (COOEt), 103.7, 102.4, 91.4, 83.5 (visible in HSO4C), 64.1 (CH2CH2), 54.8 (PO(CH3)2), 13.6 (CH3CH2); two resonances were not observed; 31P NMR (121.5 MHz, CDCl3): δ = 16.66 ppm; FTIR (neat): νmax = 2960, 2927, 2860, 2131, 1807, 1725, 1462, 1379, 1273, 1122, 1072, 1040, 962, 855, 778, 743, 705 cm⁻¹; HRMS (ESI): m/z calc for C16H18FeO3P: 398.9972 [M + Na]^+; found: 398.9974.

4.4. Ethyl (SS',6R')-6-(dimethoxyphosphoryl)-5-hydroxy-cyclohexa-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 MgSO4 and filtered. The filtrate was concentrated under reduced pressure and purified by chromatography on silica (20% acetone in Et2O) to give (±)-38 (5.6 mg, 45%) and (±)-39 (4.8 mg, 41%). (±)-38: colourless gum; Rf = 0.24 (20:80 Acetone/Et2O); HRMS m/z calc for C9H18O6P: 210.9874 [M+H]^+; found: 210.9872. (±)-39: colourless gum; Rf = 0.61 (20:80 Acetone/Et2O); HRMS (ESI): m/z calc for C9H18O6P: 398.9972 [M+H]^+; found: 398.9972.

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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.orgchem.2015.09.005.

References

