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Valuable New Cyclohexadiene Building Blocks from Cationic η^5-Iron–Carbonyl Complexes Derived from a Microbial Arene Oxidation Product

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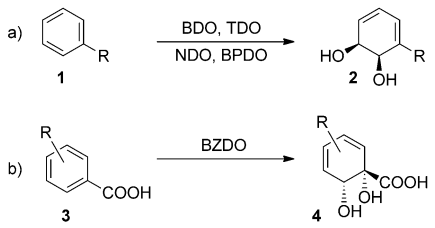
Abstract: Biooxidation of benzoic acid by *Ralstonia eutropha B9* provides an unusual cyclohexadiene carboxy diol that contains a quaternary stereocentre. Tricarbonyliron derivatives of this chiron, on treatment with acid, give two isomeric η^5-cyclohexadienyl complexes as observed by NMR spectroscopy. Both of these can be subjected to the addition of nucleophiles to provide isomeric cyclohexadiene complexes with new substituent patterns, several of which have been characterised crystallographically. De-metallation of these provides a versatile library of cyclohexadiene building blocks, the utility of which is demonstrated by formal syntheses of oseltamivir. The mechanism of product formation and its stereochemical implications are discussed, as are the procedures undertaken to establish the enantiopurity of a representative cyclohexadiene product.

Keywords: arenes · biotransformations · carbonyl ligands · cyclohexadienes · iron · oxidation

Introduction

The microbial dearomatising dihydroxylation of arenes has been known for over 40 years and the use of the cyclohexadiene *cis*-diols produced in this fashion in further synthetic transformations is an established field.[1] The densely packed, differentiated functionality of these chirons is a useful feature for applications in diverse areas, such as the synthesis of natural products,[2] pharmaceuticals,[3] carbohydrates,[4] polymers[5] and dyes.[6] Derivatives of cyclohexadiene *cis*-diols have been employed as catalysts for asymmetric cyclopropanation,[7] allylic oxidation,[7,8] *meso*-epoxide desymmetrisation,[8] aldehyde allylation[8,9] and alkene hydrogenation.[9] Applications of cyclohexadiene *cis*-diols as chiral auxiliaries[10] and in metal–organic frameworks have also been reported.[11]

The microorganisms employed for the production of cyclohexadiene *cis*-diols are most commonly those that express benzene dioxygenase (BDO), toluene dioxygenase (TDO), naphthalene dioxygenase (NDO) or biphenyl dioxygenase (BPDO). These enzymes can oxidise substituted arenes in a predictable regio- and stereoselective manner, with the sense of enantioinduction being conserved across organisms and substrates[12] (Scheme 1a; *ortho*,*meta* oxygenation). In contrast, organisms that express benzoate dioxygenase[13] (BZDO) can oxidise benzoic acids[14] in a process that exhibits not only different regioselectivity but also the opposite absolute sense of enantioinduction (Scheme 1b; *ipso*,*ortho* oxygenation). The use of *cis*-diols of type **4** has been comparatively infrequent so far.[2a,i,l,3h–i,4b,f,14a,15]



Scheme 1. Regio- and stereoselectivity of dioxygenases.

The cyclohexadiene motif in bioproducts such as **2** and **4** lends itself well to use as a ligand in tricarbonyliron(0) chemistry. Rigid cyclohexadiene ligands in which one or both of the sp^3-hybridised carbon atoms are stereocentres exhibit excellent stereoinduction upon their complexation when Lewis basic substituents are present: reports on complexes formed from diols of type **2** by the groups of Stephenson[16] and Pearson[17] describe the formation of single diastereomer only, in which the oxygen functionality is *endo* (Scheme 2). This facial selectivity has been rationalised in terms of the pre-coordination of a 16-valence-electron tetracarbonyliron fragment to one of the ligand oxygen atoms,

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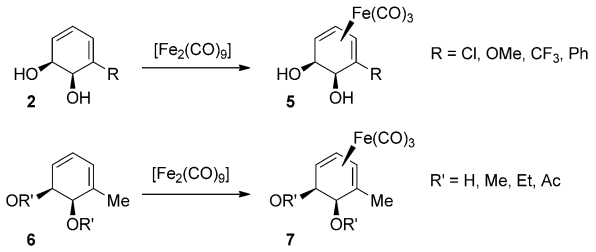
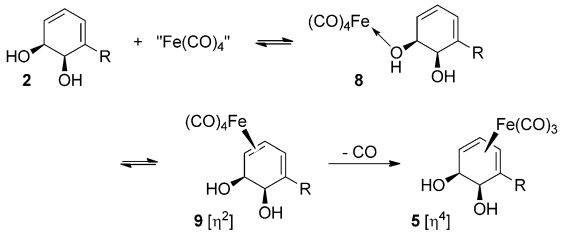


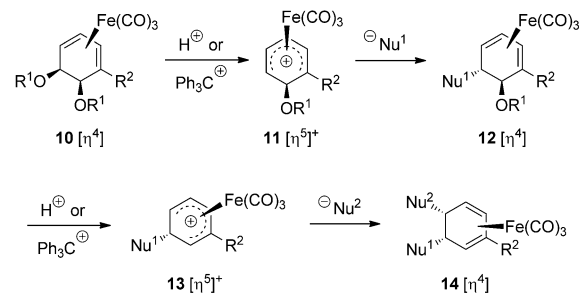
Scheme 2. Facial selectivity in iron complexation.

which serves to direct the metal to the same diene face (Scheme 3).



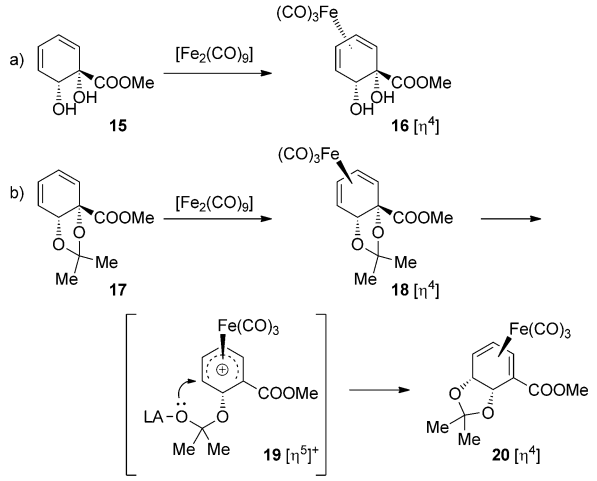
Scheme 3. Rationale for facial selectivity.

Tricarbonyl(diene)iron(0) complexes have a rich chemistry which has been the focus of much research over the years.[18] In the case of cyclohexadiene *cis*-diol complexes such as **5**, the function of the iron is twofold. Not only does it serve as a protecting group for an otherwise fragile structural motif,[19] it also allows access to new reaction manifolds by means of $[\eta^5]^+$ cyclohexadienyl cations. Indeed, an iterative $[\eta^4]\rightarrow[\eta^5]^+\rightarrow[\eta^4]\rightarrow[\eta^5]^+\rightarrow[\eta^4]$ strategy[18m,20] allows for sequential substitution of each of the two oxygen functionalities;[16f] a generalised example is shown in Scheme 4. This strategy has been employed in approaches to hippeastrine.[21] More generally,[22] $[\eta^4]\rightarrow[\eta^5]^+\rightarrow[\eta^4]\rightarrow[\eta^5]^+\rightarrow[\eta^4]$ sequences from non-arene diol starting materials have been used in the synthesis of maritidine,[23,24] lycoramine,[24] mesembrine,[25] *O*-methyljoubertiamine,[26] stemodinone,[27] antiostatins,[28] clausines,[29] oxydimurrayafoline,[30] lavanduquinocin,[31] streptoverticillin[32] and numerous other syntheses of carbazole alkaloids[33] that demonstrate the power of dienyliron electrophiles. They have also been used in an approach to lycorine[34] and in the construction of functionalised medium rings,[35] quaternary centres,[36] spirocycles[37] and indole derivatives.[38]



Scheme 4. Sequential substitution of -OR^1 groups.

We have recently reported on the previously unexplored organometallic chemistry of arene diols of type **4**. Specifically, the diene diol methyl ester **15** was treated with $[Fe_2(CO)_9]$ to give **16** (in which the ester is *exo*[39]) as the only product (Scheme 5a).[40] Ligand **15** differs from **2** and **6** in that both diene faces present Lewis basic functionality toward an incipient tetracarbonyliron fragment. As such, it may be regarded as a "competition ligand"; only one previous report describes a complex formed from such a ligand.[41] The formation of **16** as the sole diastereomer shows a diol to be a markedly more effective directing group than a methyl ester in this context.[42] In an attempt to access complexes in which the diol was in the *exo* position, we prepared acetonide **17**. As expected, the acetonide reduced the directing ability of the diol and complex **20** was formed, in which the acetonide was indeed *exo* (Scheme 5b). Surprisingly, a ligand isomerisation occurred, resulting in the conjugation of the diene and ester groups in **20**.[43]



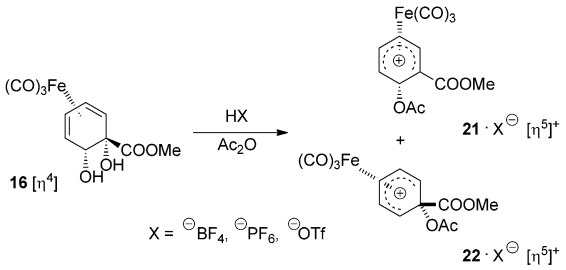
Scheme 5. Organometallic chemistry of dienes of type **4**.

We proposed that the formation of **20** occurs by an $[\eta^4]\rightarrow[\eta^5]^+\rightarrow[\eta^4]$ process beginning with the formation of the expected product, complex **18**. Subsequent Lewis acid mediated isomerisation via the cyclohexadienyl $[\eta^5]^+$ intermediate **19** and recombination of the pendent nucleophile ω to the ester would provide **20** (Scheme 5b). Comparable isomerisations have been reported for CpCo–diene complexes (Cp = cyclopentadiene).[44,45] It should be noted that complex **20** is oxygenated with the opposite absolute configuration to complexes of type **5**. This is of synthetic significance as it allows access to the antipodal series of *ortho,meta*-arene diols that are not directly accessible by biotransformation. Encouraged by these results, we undertook further studies on $[\eta^4]\rightarrow[\eta^5]^+\rightarrow[\eta^4]$ derivatisations of **16**. To diversify rapidly the ligand

structure, we sought to employ the intermolecular addition of nucleophiles rather than intramolecular addition, as per the formation of **20**. The results of these studies are reported herein.

Results and Discussion

To form stable cyclohexadienyl $[\eta^5]^+$ complexes from **16** it was necessary to derivatise the hydroxyl groups, as it has been established that tricarbonyliron(0)cyclohexadienyl complexes that contain an unprotected 6-*endo*-hydroxyl group can readily decompose by aromatisation of the cyclohexadienyl ligand.[16e,g,41] Accordingly, we adopted the Pearson procedure, which involves the use of acetic anhydride as the solvent.[46] This serves a dual purpose: to protect the hydroxyl groups as acetates, and to act as a desiccant when aqueous acids such as $HBF_{4(aq)}$ or $HPF_{6(aq)}$ are used to promote deacetoxylation. In the case of **16**, this procedure could potentially give rise to two regioisomeric cations, **21** and **22**, depending on which C–O bond is cleaved (Scheme 6).



Scheme 6. Regioisomeric cations arising from **16**.

In the case of complexes of type **10** (Scheme 4), varying degrees of regioselectivity have been reported for the corresponding $[\eta^4]\rightarrow[\eta^5]^+$ deacetoxylation reactions. When the diene substituent R^2 is strongly electron withdrawing or donating, loss of the distal acetate (and formation of **11**) is favoured.[16b,17] In contrast, the reaction is less regioselective if $R^2=Me$.[16e] However, none of these literature examples provide direct precedent for the reaction depicted in Scheme 6 because in complex **16**, the ester substituent is not conjugated with the diene. Thus, at the outset, it was unclear whether product **21** or **22** would predominate.

To observe in situ the formation of $[\eta^5]^+$ cyclohexadienyl species from **16**, we used real-time ^{1}H NMR monitoring with solvent suppression (Figure 1). The NMR spectra are highly diagnostic because at 500 MHz no overlap of ring methine resonances is observed and every ring proton may be individually assigned for all three species present. Even after 5 min, the neutral $[\eta^4]$ precursor **23** was seen to be the

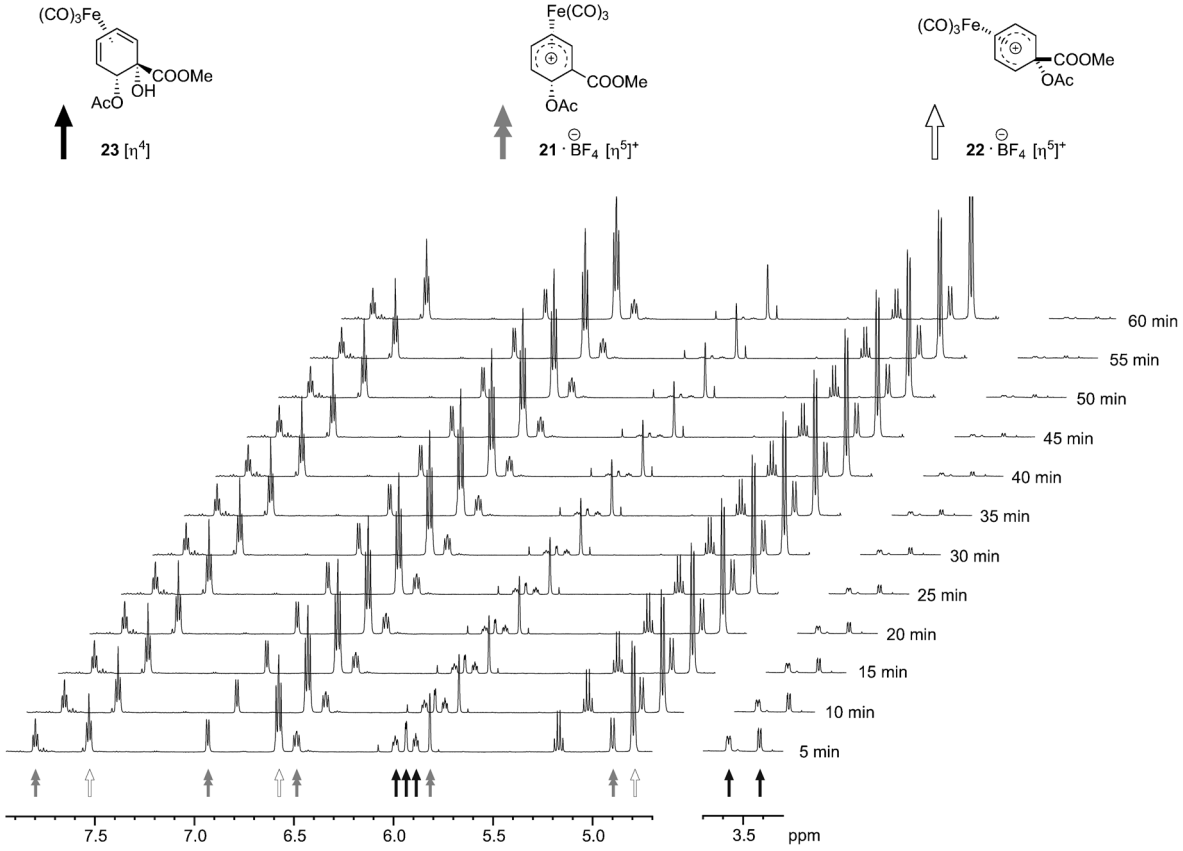


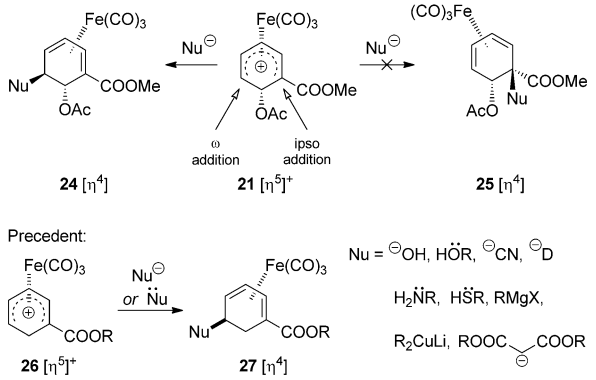
Figure 1. ^{1}H NMR spectra showing the real-time formation of **21** and **22**. Spectra were acquired at 5 min intervals in Ac_2O with $HBF_4{\cdot}OEt_2$ (5 equiv) at 298 K, and by employing solvent suppression.

minor component of the mixture; the methine resonances for **23** are indicated with solid black arrows. The signals for the diene termini in **23** are the only methine protonss observed upfield of $\delta = 4.0$ ppm, whereas the corresponding ligand terminus resonances for **21** (grey double arrows) and **22** (white arrows) are shifted downfield due to the comparatively electron-poor nature of these complexes.

It can clearly be seen that after 1 h, **23** has been consumed and only resonances for cations **21** and **22** are observed, with **22** being the major component of the reaction mixture (≈3:1 ratio). Whereas **21** and **23** each exhibit five distinct methine resonances, cation **22** exhibits three resonances, the integrals of which are in a ratio of 2:2:1, clearly illustrating that this complex possesses a plane of symmetry that bisects the cyclohexadienyl ring. It must be stressed that whereas the starting material **16** is homochiral, stereochemical information is lost upon formation of the achiral cation **22**.

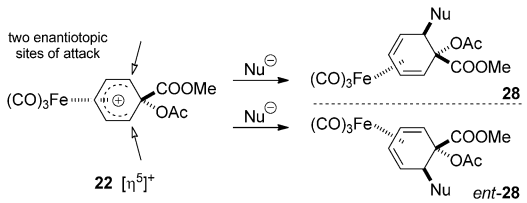
Having established the viability of forming both **21** and **22**, we next examined their reactivity towards nucleophiles. In general, the major products of nucleophilic additions to tricarbonyliron(0) cyclohexadienyl $[\eta^5]^+$ complexes are those resulting from attack of the nucleophile to the *exo* face of the ring (i.e., the opposite side of the ring to the iron atom).[18m,47] Few examples of *endo* attack and cases of equilibration to *endo*/*exo* product mixtures by reversible addition are known.[48]

Regarding the regioselectivity of the addition reaction, incorporation of the nucleophile should typically occur at one of the two dienyl termini.[49] For cation **21**, two regioisomeric products are therefore possible by addition at the position either *ipso* or ω to the ester.[50] Literature precedent shows a terminal ester substituent to be strongly ω-directing for the nucleophilic addition of hydroxide,[51] alcohols,[52–54] amines,[54] thiols,[54] malonate,[54,55] cyanide,[56] deuteride,[56] cuprates[56] and Grignard reagents,[56] as well as for S_EAr reactions of electron-rich arenes.[53,54] Thus, additions to cation **21** were expected to furnish products of type **24** (Scheme 7).



Scheme 7. Possible products of nucleophilic addition to **21**.

For cation **22**, the regiochemistry of addition is more straightforward as the two dienyl termini are enantiotopic. Thus, the addition of a nucleophile will necessarily give an adduct (±)-**28**, which is racemic (Scheme 8). The reaction sequence **16**→**22**→**28** is a homochiral $[\eta^4]$→achiral $[\eta^5]^+$→racemic $[\eta^4]$ sequence; analogous sequences for other



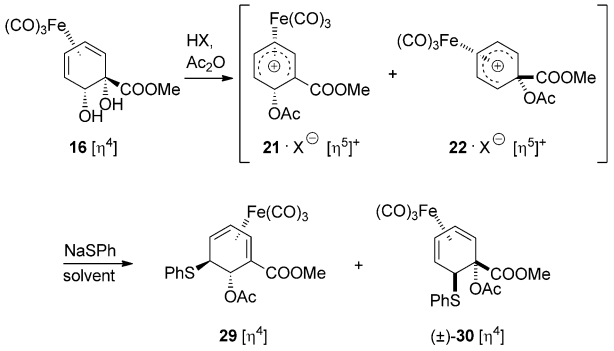
Scheme 8. Formation of racemic products from **22**.

$Fe(CO)_3$ cyclohexadiene complexes have also been reported.[57]

We chose sodium thiophenolate as a prototypical nucleophile with which to study additions to cations **21** and **22**. Complex **16** was treated with a variety of acids in Ac_2O, followed by precipitation by addition of diethyl ether and filtration. The mixture of cations obtained was re-dissolved in either THF or acetonitrile and treated with NaSPh. The results are summarised in Table 1.

Yields varied significantly with the choice of solvent and acid. In each instance, (±)-**30** was the major product, as anticipated from the in situ NMR data that showed **22** to be the major cation. However, with the exception of entries 7

Table 1. Optimisation of cation generation and nucleophile addition to form thiophenolate adducts.[a]



Entry	Acid	Solvent	Yield of **29** [%]	Yield of (±)-**30** [%]
1	TFA	THF	4	25
2	TFA	MeCN	3	20
3	TfOH	THF	3	36
4	TfOH	MeCN	6	38
5[b]	HPF_6	THF	6	45
6	HPF_6	MeCN	0	23
7	HBF_4	THF	4	14
8	HBF_4	MeCN	5	13
9	$HBF_4{\cdot}OEt_2$	THF	0	57
10	$HBF_4{\cdot}OEt_2$	MeCN	0	34

[a] Acid (10.0 equiv), Ac_2O, −10 °C, 1 h, then precipitation, filtration, solvation in an alternative solvent, NaSPh (4.3 equiv), 0 °C, 1 h. [b] A by-product was also obtained in 8% yield.[58] TFA = trifluoroacetic acid, Tf = trifluoromethanesulfonyl.

and 8 (Table 1), the product ratio (+)-**29**/(±)-**30** was always less than the NMR cation ratio **21**/**22**. Indeed, for entries 6, 9 and 10 (Table 1), product **29** was not isolated at all. These results may be due to the instability of cation **21** (see below). Crystals of (±)-**30** that were suitable for X-ray structure determination were obtained from the diffusion of hexane into a solution of (±)-**30** in dichloromethane (Figure 2).

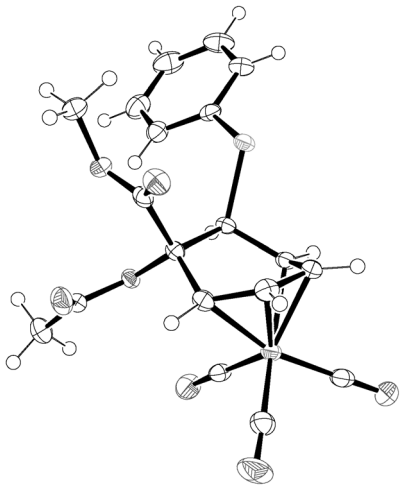


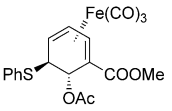
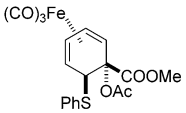
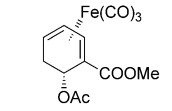
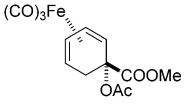
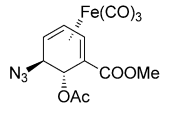
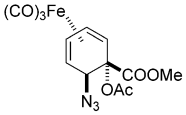
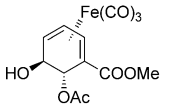
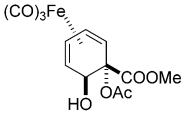
Figure 2. Solid-state structure of (±)-**30**. Ellipsoids are represented at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

Having ascertained that both cations **21** and **22** were reactive electrophiles, we screened several other nucleophiles to determine the scope of the addition reaction (Table 2). In each instance, cations were generated by treatment with HBF_4·OEt_2, on the basis of the results in Table 1. However, for each entry in Table 2, the conditions for the subsequent nucleophile addition were varied on the basis of (limited) optimisation studies.

Yields for the addition of other nucleophiles were slightly lower than for thiophenolate; the comparatively mediocre reactivity of hydroxide in addition reactions to $Fe(CO)_3$–cyclohexadienyl cations has been noted previously.[59] Crystals of (±)-**32** that were suitable for X-ray structure determination were obtained from the diffusion of hexane into a solution of (±)-**32** in ethyl acetate (Figure 3).

The hydroxide adduct (±)-**36** did not furnish crystals suitable for X-ray diffraction. However, basic methanolysis of (±)-**36** gave the diol (±)-**37**. Crystals of (±)-**37** of sufficient quality for analysis were obtained by slow evaporation of a solution of (±)-**37** in ethyl acetate (Scheme 9, Figure 4). The structure confirmed once again the *trans* relationship of the introduced nucleophile and the residual ring oxygenation. The structure of **37** is significant because it is a protected form of an arene *trans*-diol. Arene *trans*-diols are not available from the direct biotransformation of arenes with arene dioxygenase enzymes, although they may be accessed indirectly by epoxidation with mono-oxygenases and subsequent epoxide opening.[60] Multi-step chemo-enzymatic approaches

Table 2. Reactivities of diverse nucleophiles towards cations **21** and **22**.[a]

Entry	Nu^-	Product from **21** (Yield [%])		Product from (±)-**22** (Yield [%])	
1[b]	NaSPh	 **29** [η^4]	(6)	 (±)-**30** [η^4]	(45)
2[c]	$NaBH_4$	 **31** [η^4]	(4)	 (±)-**32** [η^4]	(31)
3[c]	NaN_3	 **33** [η^4]	(5)	 (±)-**34** [η^4]	(34)
4[c]	NaOH	 **35** [η^4]	(10)	 (±)-**36** [η^4]	(25)

[a] For each entry, **16** was treated with HBF_4·OEt_2 (4 equiv) in Ac_2O at −10 °C for 1 h, then the cation was precipitated by using Et_2O. [b] THF, −78 °C to RT, 1 h. [c] MeCN, 0 °C to RT, 1 h.

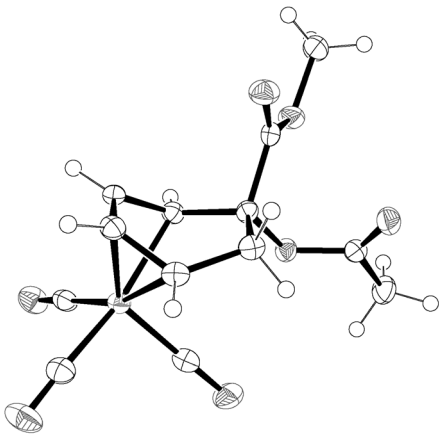
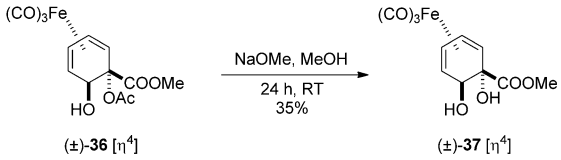


Figure 3. Solid-state structure of (±)-**32**. Ellipsoids are represented at 50% probability. H atoms are shown as spheres of arbitrary radius.



(±)-**36** [η^4] (±)-**37** [η^4]

Scheme 9. Deacetylation of (±)-**36**.

to arene *trans*-diols have been reported,[61] and an approach that involves $[Fe(CO)_3]$ complexes has been alluded to previously but is not described in any detail in the literature.[62]

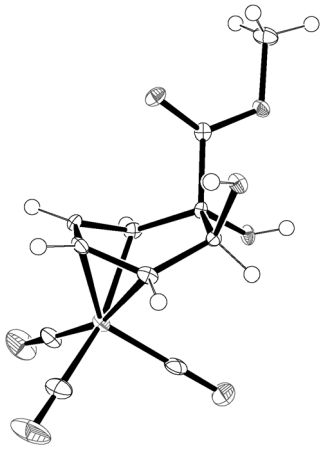
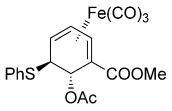
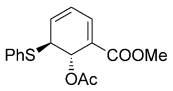
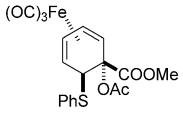
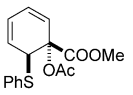
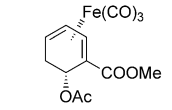
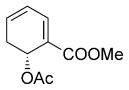
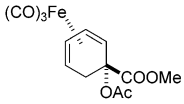
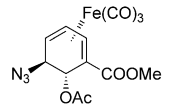
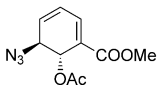
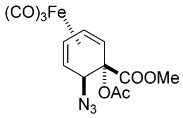
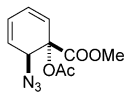
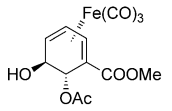
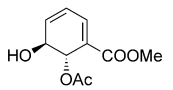
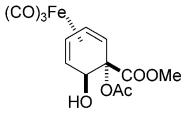
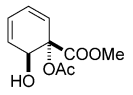


Figure 4. Solid-state structure of (±)-**37**. Ellipsoids are represented at 50% probability. H atoms are shown as spheres of arbitrary radius.

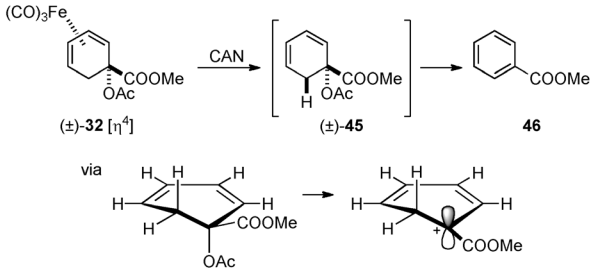
With a variety of complexes in hand, we sought to promote their de-metallation to recover the modified cyclohexadiene ligands (Table 3). Of the reported methods for $[Fe(CO)_3]$ de-complexation, oxidation with ceric ammonium nitrate (CAN)[63] proved superior to the use of trimethylamine-*N*-oxide[64] for these substrates, allowing access to the new cyclohexadienes **38**–**44** in good yield (Table 3). As shown in Table 3, entry 4, the attempted de-metallation of complex (±)-**32** did not give the expected cyclohexadiene product (±)-**45**. Instead, methyl benzoate **46** was recovered (Scheme 10). We rationalise this finding as follows: **46** arises from initial formation of the expected (±)-**45**, which then undergoes an unusually facile re-aromatisation by the elimination of acetic acid. The spontaneous re-aromatisation of (±)-**45** is in contrast to that of cyclohexadienes **38**–**44** and may be explained by the fact that only **45** is able to achieve a conformation in which the C1 acetate and a C6 proton have a dihedral angle of approximately 180°. The fact that arene *cis*-diols re-aromatise at far greater rates than the corresponding arene *trans*-diols upon their exposure to acid has previously been rationalised in this manner: a conformation such as that depicted for **45** leads to a cyclohexadienyl E_1 intermediate in which the pseudo-axial hydrogen atom is ideally aligned for hyperconjugation with a p orbital of the carbocation intermediate.[65]

We next sought to determine the enantiopurity of the adducts derived from $[\eta^5]^+$ cyclohexadienyl cation **21**. Because stereochemical information is not lost upon formation of the (non-symmetric) cation **21**, the resultant adducts (**29**, **31**, **33** and **35**) were expected to be isolated as single enantiomers. However, the possibility that cation **21** might undergo racemisation by equilibration[66] with achiral cation **22** could not be excluded. Such an equilibration might plausibly occur by participation of the neighbouring acetoxy functionality, although this would involve the *endo* attack of the tethered nucleophile (Scheme 11). Accordingly, we deemed it necessary to determine the enantiomeric excess of an adduct derived from cation **21**.

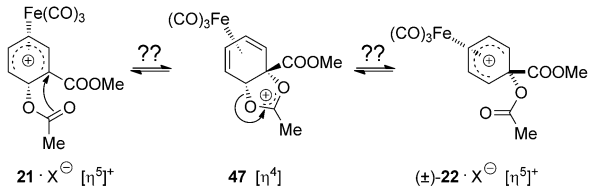
Table 3. De-metallation of complexes **28**–**35** with CAN.

Entry	Substrate	Product	Yield [%]
1[a,b]	 **29** [η^4]	 **38**	91
2[a,b]	 (±)-**30** [η^4]	 (±)-**39**	85
3[a,c]	 **31** [η^4]	 **40**	63
4[a]	 (±)-**32** [η^4]	–	0
5[a,d]	 **33** [η^4]	 **41**	63
6[a,e]	 (±)-**34** [η^4]	 (±)-**42**	64
7[a,b]	 **35** [η^4]	 **43**	53
8[a,f]	 (±)-**36** [η^4]	 (±)-**44**	100

[a] $Ce(NH_4)_2(NO_3)_6$ (3 equiv), acetone, 0°C. [b] 5 min. [c] 50 min. [d] 3 h. [e] 4 h. [f] 25 min.

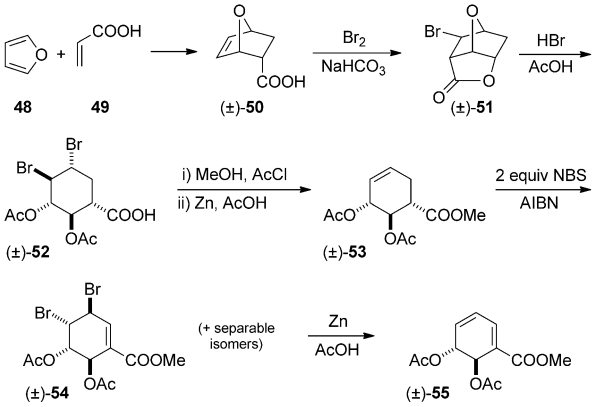


Scheme 10. Facile rearomatisation of **45**.



Scheme 11. Mechanism for the potential racemisation of **21**.

Measurements of enantiomeric excess by chiral HPLC were not possible for the new adducts **29**, **31**, **33** and **35** as racemic material was not available for comparison. Similarly, the corresponding de-metallated cyclohexadienes **38**, **40**, **41** and **43** are also previously unreported as either single enantiomers or racemates. However, acetylation of the de-metallated hydroxide adduct **43** gave the diacetate derivative **55**, which has been reported as a racemate by Ogawa et al.[67] (Scheme 12).



Scheme 12. The Ogawa et al. preparation of racemic (±)-**55**.

Preparation of a racemic standard of (±)-**55** by the Ogawa protocol allowed for assessment of the enantiomeric excess of the chemoenzymatically produced **55** by chiral HPLC (Figure 5), which was indeed produced in >99% *ee*. Thus, the mechanism for potential racemisation shown in Scheme 11 is negligible and, by inference, the adducts **29**, **31**, **33** and **35**, derived from cation **21**, may be assumed to be enantiopure.

We next sought to expand the method described above to an $[\eta^4]\rightarrow[\eta^5]^+\rightarrow[\eta^4]\rightarrow[\eta^5]^+\rightarrow[\eta^4]$ sequence, that is, to promote the sequential substitution of both of the enzyme-derived hydroxy groups. To demonstrate the utility of such a sequence, we undertook a concise formal synthesis of the anti-influenza agent oseltamivir **56** (Scheme 13). Oseltamivir has been the target of numerous syntheses,[68] and approaches initiated by microbial arene dihydroxylation have been reported by the groups of Hudlický,[3a–d] Banwell[3e] and Fang.[3f] Furthermore, a route employing tricarbonyliron complexes has been reported by Kann et al.[52] To access oseltamivir from *ipso*,*ortho*-diol **4** requires double-bond

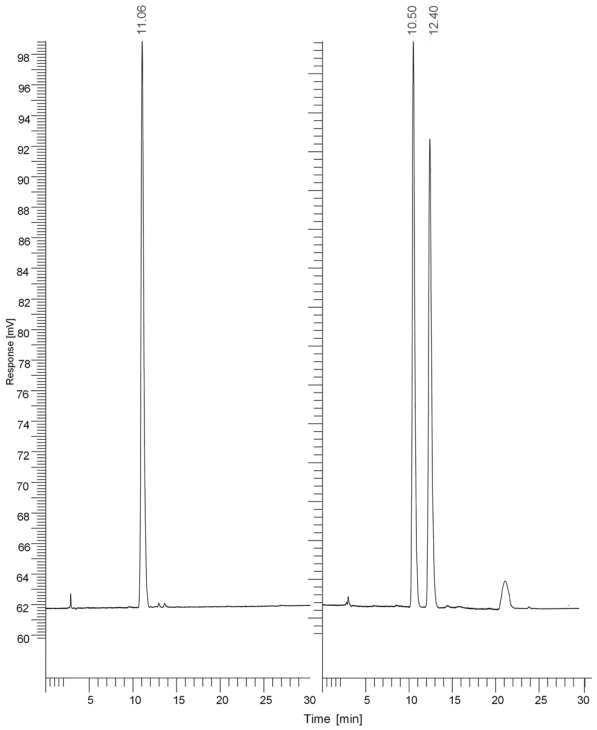
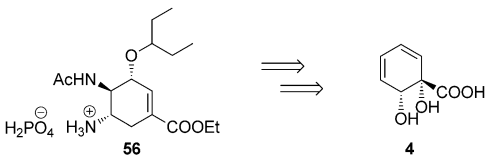


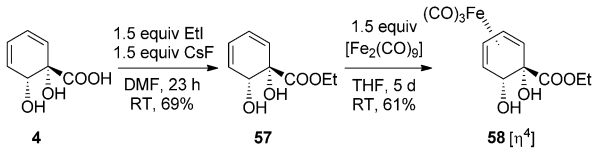
Figure 5. Chromatograms for **55**. Left: Sample prepared by the chemoenzymatic route described herein. Right: Racemic sample prepared by the protocol described by Ogawa et al. Conditions: ChiralCel OD-I column, isocratic elution, hexane/*i*PrOH (95:5), 1.0 mL min^{-1}, λ = 254 nm, t_R1 = 10.50 min, t_R2 = 12.40 min.



Scheme 13. Access to oseltamivir from the *ipso*,*ortho*-diol **4**.

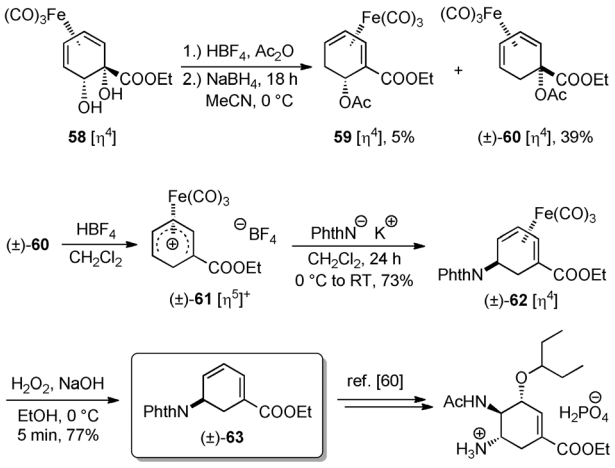
transposition, which can be brought about by a $[\eta^4]\rightarrow[\eta^5]^+\rightarrow[\eta^4]$ sequence. It also requires the use of a different iron complex as the starting material because of the different substituents: **16** contains a methyl ester, whereas **56** contains an ethyl ester. Accordingly, the carboxylate alkylation of **4** was undertaken with ethyl iodide and caesium fluoride as an additive,[69] followed by treatment with nonacarbonyldiiron to provide complex **58** as a single isomer (Scheme 14).

With the ethyl complex **58** in hand, the formation of the corresponding cations and their reaction with sodium borohydride proceeded as in the case of the methyl complex **16**.



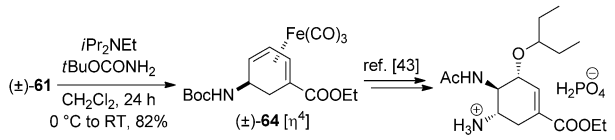
Scheme 14. Preparation of the ethyl ester complex **58**.

Complex (±)-**60** was treated with acid for a second time to remove the second acetoxy group and provide cation (±)-**61**. Treatment of (±)-**61** with potassium phthalimide then gave complex (±)-**62**. The regioselectivity of this addition agrees with precedent (Scheme 7). Finally, de-metallation with basic hydrogen peroxide[70] gave (±)-**63** (Scheme 15), a reported intermediate in the route to oseltamivir described by Trost et al.[71] Access to the $[\eta^5]^+$ complex (±)-**61** also



Scheme 15. Formal synthesis of oseltamivir. Phth = phthaloyl.

allows for the realisation of another formal synthesis: addition of a different nitrogen nucleophile (*tert*-butyl carbamate[72]) gave complex (±)-**64**, which is a reported intermediate in the Kann route to oseltamivir[52] (Scheme 16).



Scheme 16. Alternative formal synthesis of oseltamivir. Boc = *tert*-butoxycarbonyl.

Conclusion

We have achieved the synthesis of a diverse library of new cyclohexadiene building blocks. This was accomplished by the rapid diversification of a single bio-derived iron–carbonyl complex by means of nucleophile addition to cationic $[\eta^5]^+$ complexes. The extension of this approach to a second diversification step has also been demonstrated. The enantiopurity of a representative building block was established by comparison with a known racemic material, which was synthesised independently. We anticipate that the building blocks reported herein will find multiple applications in synthesis.

Experimental Section

General synthetic procedures and instrumentation: Reactions were carried out under an atmosphere of nitrogen. Solvents were dried and degassed by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400–7 solvent-purification system. Acetic anhydride and acetone were laboratory-reagent-grade solvents and were not specially dried prior to use. Petrol refers to petroleum ether, b.p. 40–60 °C. TLCs were performed by using aluminium-backed plates precoated with Alugram SIL G/UV and visualized by UV light (254 nm) and/or $KMnO_4$ followed by gentle warming. Flash column chromatography was carried out by using 60 Å silica gel (particle size 35–70 μm) purchased from Fisher Scientific Ltd. All reagents were purchased from the Sigma–Aldrich Chemical Co. or Fisher Scientific Ltd. and were used without further purification. Nonacarbonyldiiron was dispensed in a glovebox. IR spectra were recorded on a Perkin–Elmer Spectrum 100 FTIR spectrometer with a universal ATR sampling accessory; absorbances are quoted as $\tilde{\nu}$ in cm^{-1}. NMR analysis was done on Brüker Avance 250, 300, 400 or 500 MHz instruments at 298 K, unless otherwise specified. Mass spectra were recorded with a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Brüker Daltonics). 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 per 100 mL.

CCDC-865581 ((±)-**30**), CCDC-865582 ((±)-**32**) and CCDC-865583 ((±)-**37**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Formation of cations 21 and 22: Tetrafluoroboric acid diethyl etherate (521 mg, 438 μL, 3.22 mmol, 10.0 equiv) was added to a stirred solution of $[\eta^4]$ complex **16** (100 mg, 0.322 mmol, 1.00 equiv) in acetic anhydride (3.2 mL) at −10 °C and stirred at this temperature for 1 h. Pre-cooled Et_2O (60 mL) was added dropwise to the reaction mixture, forming a light-yellow precipitate. This was filtered by using suction and washed with cold Et_2O (3×5 mL). Concentration of the mother liquor and recrystallisation from *t*BuOMe gave a small quantity of additional product; the crude cation mixture was used immediately in the next step.

General procedure for the formation of adducts 29 to 36: The relevant nucleophile (5.00 equiv with respect to starting complex **16**) was added to a solution of the crude cation mixture (of **21** and **22**, as prepared above) in THF or MeCN (5 mL) at the specified temperature. The reaction mixture was stirred for 1 h, then quenched by addition of H_2O. The product was extracted with EtOAc or Et_2O (3×20 mL). The organic layers were combined, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate) to give the final products **29**–**36**.

*Sodium thiophenolate as a nucleophile: formation of **29** and (±)-**30***: In accordance with the general procedure, the use of THF at −78 °C to RT with **16** (82 mg) gave **29** as a yellow oil (7.3 mg, 6%) and (±)-**30** as a beige solid (52.4 mg, 45%). **29**: $R_f = 0.15$ (10:90 EtOAc/hexane); $[\alpha]_D^{25} = +20$ ($c = 0.05$ in CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.44$–7.42 (2H, m; *o*-Ar-H), 7.32–7.29 (3H, m; *p*-Ar-H and *m*-Ar-H), 5.91 (1H, d, $J = 4.0$ Hz; H-6), 5.41 (1H, t, $J = 5.0$ Hz; H-5), 5.24 (1H, s; H-2), 3.65 (3H, s; -$COOCH_3$), 3.30 (1H, s; H-4), 3.26 (1H, brs; H-3), 2.05 ppm (3H, s; -$OC(O)CH_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 208.9$ ([$Fe(CO)_3$]), 171.0, 169.3, 134.3, 129.7, 129.0, 128.4, 90.5, 83.0, 72.8, 64.8, 60.8, 55.2, 52.0, 21.0 ppm; FTIR (neat): $\tilde{\nu}_{max} = 2061$, 1991, 1749, 1717, 1438, 1370, 1272, 1229, 1097, 1026, 693, 143 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{16}FeO_7S$: 466.9864 $[M+Na]^+$; found: 466.9861; elemental analysis calcd (%) for $C_{19}H_{16}FeO_7S$: C 51.37, H 3.63; found: C 51.3, H 3.64. (±)-**30**: $R_f = 0.28$ (10:90 EtOAc/hexane). M.p. 117–118 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.39$–7.35 (2H, m; *o*-Ar-*H*), 7.33–7.27 (3H, m; *p*-Ar-H and *m*-Ar-H), 5.64 (1H, ddd, $J = 6.0$, 4.0, 1.5 Hz; H-5), 5.39 (1H, td, $J = 5.5$, 1.0 Hz; H-4), 3.77 (1H, d, $J = 6.5$ Hz; H-6), 3.66 (3H, s; -$COOCH_3$), 3.64 (1H, d, $J = 4.0$ Hz; H-2), 3.29 (1H, ddt, $J = 5.0$, 3.5, 1.5 Hz; H-3), 2.18 (3H, s; -$OC(O)CH_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 210.0$ ([$Fe(CO)_3$]), 170.2, 168.9, 136.2, 131.0, 129.1, 127.2, 87.3, 86.6, 83.9, 61.1, 58.9, 57.6, 52.7, 21.5 ppm; FTIR (neat): $\tilde{\nu}_{max} = 3067$, 2951, 2052, 1967, 1739, 1582, 1481, 1438, 1367, 1276, 1243, 1219, 1138, 1086, 1061,

1049, 1025, 987, 948, 909, 866, 809, 732, 691 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{16}FeO_7S$: 466.9864 $[M+Na]^+$; found: 466.9850.

*Sodium borohydride as a nucleophile: formation of **31** and (±)-**32***: In accordance with the general procedure, the use of MeCN at 0 °C to RT with **16** (200 mg) gave **31** as a yellow solid (9.5 mg, 4%) and (±)-**32** as a yellow solid (68.8 mg, 31%). **31**: R_f = 0.30 (20:80 EtOAc/hexane); m.p. 67–69 °C; $[\alpha]_D^{25}$ = +280 (*c* = 0.1 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.94 (1H, d, *J* = 3.0 Hz; H-6), 5.52 (1H, t, *J* = 5.0 Hz; H-5), 5.03 (1H, d, *J* = 6.5 Hz; H-2), 3.68 (3H, s; -$COOCH_3$), 3.20 (1H, br s; H-4), 2.09 (1H, dd, *J* = 16.0, 6.5 Hz; H-3), 2.07 (3H, s; -$OC(O)CH_3$), 1.58 ppm (1H, dd, *J* = 16.0, 3.5 Hz; H-3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 209.4 ($[Fe(CO)_3]$), 171.7, 170.2, 90.3, 84.5, 77.4, 68.1, 58.7, 51.9, 34.3, 21.2 ppm; FTIR (neat): $\tilde{\nu}_{max}$ = 2952, 2850, 2055, 1972, 1737, 1713, 1583, 1435, 1368, 1343, 1270, 1235, 1132, 1097, 1042, 1029, 991, 969, 894, 865, 802, 775, 715, 685 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{12}FeO_7$: 358.9830 $[M+Na]^+$; found: 358.9834; elemental analysis calcd (%) for $C_{13}H_{12}FeO_7$: C 46.46, H 3.60; found: C 46.6, H 3.71. (±)-**32**: R_f = 0.45 (20:80 EtOAc/hexane); m.p. 89–91 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.46 (1H, t, *J* = 5.5 Hz; H-4), 5.35 (1H, ddd, *J* = 6.0, 4.0, 1.0 Hz; H-5), 3.65 (3H, s; -$COOCH_3$), 3.16 (1H, dd, *J* = 4.0, 2.0 Hz; H-3), 3.05 (1H, d, *J* = 6.5 Hz; H-6), 2.71 (1H, dd, *J* = 16.0, 1.0 Hz; H-2), 2.07 (3H, s; -$OC(O)CH_3$), 1.91 ppm (1H, dd, *J* = 16.5, 3.5 Hz; H-2); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 210.5 ($[Fe(CO)_3]$), 171.8, 170.1, 87.1, 82.3, 81.4, 61.5, 60.4, 52.9, 39.9, 21.0 ppm; FTIR (neat): $\tilde{\nu}_{max}$ = 2957, 2048, 1961, 1735, 1436, 1371, 1330, 1273, 1248, 1200, 1125, 1056, 1014, 969, 947, 899, 865, 843, 810, 762, 674 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{12}FeO_7$: 358.9830 $[M+Na]^+$; found: 358.9825.

*Sodium azide as a nucleophile: formation of **33** and (±)-**34***: In accordance with the general procedure, the use of THF at 0 °C to RT with **16** (195 mg) gave **33** as a light-yellow oil (12.4 mg, 5%) and (±)-**34** as a yellow solid (81.4 mg, 34%). **33**: R_f = 0.43 (20:80 EtOAc/hexane); $[\alpha]_D^{25}$ = +430 (*c* = 0.1 in CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.09 (1H, dd, *J* = 4.5, 1.0 Hz; H-6), 5.67 (1H, t, *J* = 5.0 Hz; H-5), 4.95 (1H, s; H-2), 3.68 (3H, s; -$COOCH_3$), 3.58 (1H, d, *J* = 4.5 Hz; H-3), 3.14 (1H, td, *J* = 5.5, 1.0 Hz; H-4), 2.11 ppm (3H, s; -$OC(O)CH_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 208.4 ($[Fe(CO)_3]$), 170.9, 169.6, 91.7, 82.9, 73.0, 66.9, 63.6, 55.8, 52.2, 21.0 ppm; FTIR (neat): $\tilde{\nu}_{max}$ = 2955, 2059, 1982, 1746, 1713, 1456, 1435, 1369, 1323, 1275, 1225, 1151, 1099, 1032, 971, 926, 872, 814, 775, 745 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{11}FeN_3O_7$: 399.9844 $[M+Na]^+$; found: 399.9846; elemental analysis calcd (%) for $C_{13}H_{11}FeN_3O_7$: C 44.41, H 2.94, N 11.14; found: C 41.6; H 3.00, N 10.7. (±)-**34**: R_f = 0.56 (20:80 EtOAc/hexane); m.p. 124–126 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.69 (1H, t, *J* = 4.5 Hz; H-5), 5.59 (1H, t, *J* = 5.0 Hz; H-4), 3.90 (1H, d, *J* = 3.5 Hz; H-2), 3.72 (3H, s; -$COOCH_3$), 3.54 (1H, d, *J* = 6.0 Hz; H-6), 3.05 (1H, t, *J* = 4.5 Hz; H-3), 2.15 ppm (1H, s; -$OC(O)CH_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 209.4 ($[Fe(CO)_3]$), 170.0, 168.1, 86.9, 85.1, 84.2, 68.0, 57.1, 55.2, 53.0, 21.3 ppm; FTIR (neat): $\tilde{\nu}_{max}$ = 2956, 2054, 1971, 1740, 1450, 1435, 1369, 1331, 1222, 1138, 1063, 1041, 1012, 993, 946, 915, 869, 812, 766, 733, 716, 672, 649 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{11}FeN_3O_7$: 399.9844 $[M+Na]^+$; found: 399.9829; elemental analysis calcd (%) for $C_{13}H_{11}FeN_3O_7$: C 44.41, H 2.94, N 11.14; found: C 41.5, H 2.97, N 10.7.

*Sodium hydroxide as a nucleophile: formation of **35** and (±)-**36***: In accordance with the general procedure, the use of MeCN at 0 °C to RT with **16** (233 mg) and an aqueous solution of NaOH (0.1 M) as the nucleophile gave **35** as a yellow oil (27.6 mg, 10%) and (±)-**36** was isolated as a light-yellow foam (64.8 mg, 25%). **35**: R_f = 0.26 (40:60 EtOAc/petrol); $[\alpha]_D^{25}$ = +190 (*c* = 0.1 in CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.07 (1H, dd, *J* = 4.5, 1.0 Hz; H-6), 5.61 (1H, t, *J* = 5.5 Hz; H-5), 4.66 (1H, s; H-2), 3.87 (1H, br s; H-3), 3.68 (3H, s; -$COOCH_3$), 3.12 (1H, t, *J* = 5.5 Hz; H-4), 2.70 (1H, d, *J* = 3.0 Hz; -OH), 2.12 ppm (3H, s; -$OC(O)CH_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 171.42, 171.39, 91.3, 83.9, 76.9, 76.6, 61.7, 59.2, 52.1, 21.1 ppm; FTIR (neat): $\tilde{\nu}_{max}$ = 3412, 2059, 1984, 1750, 1713, 1436, 1374, 1271, 1237, 1100, 1034, 969, 919, 873, 775, 685 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{12}O_8Fe$: 374.9782 $[M+Na]^+$; found 374.9774; elemental analysis calcd (%) for $C_{13}H_{12}FeO_8$: C 44.35, H 3.44; found: C 43.9, H 3.64. (±)-**36**: R_f = 0.36 (40:60 EtOAc/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.61 (1H, ddd, *J* = 6.0, 4.0, 1.5 Hz; H-5), 5.47 (1H, t, *J* = 5.5 Hz; H-4), 4.17 (1H, dd, *J* = 7.0, 3.5 Hz; H-2), 3.70 (3H, s; -$COOCH_3$), 3.20 (1H, d, *J* = 6.5 Hz; H-6), 3.13 (1H, ddd, *J* = 5.0, 3.5, 1.5 Hz; H-3), 2.71 (1H, d, *J* = 7.0 Hz; -OH), 2.15 ppm (3H, s; -$OC(O)CH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 209.9 ($[Fe(CO)_3]$), 170.6, 169.8, 85.2, 85.1, 84.0, 77.6, 61.1, 55.7, 53.0, 21.2 ppm; FTIR (neat): $\tilde{\nu}_{max}$ = 3421, 2956, 2923, 2853, 2050, 1966, 1739, 1714, 1432, 1367, 1333, 1270, 1236, 1205, 1136, 1101, 1069, 1049, 1025, 992, 964, 929, 909, 872, 814, 763, 734, 705, 674 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{12}O_8Fe$: 374.9782 $[M+Na]^+$; found: 374.9779; elemental analysis calcd (%) for $C_{13}H_{12}FeO_8$: C 44.35, H 3.44; found: C 44.7, H 3.56.

Methanolysis of (±)-36 to give (±)-37: Solid sodium methoxide (118 mg, 3.68 mmol, 20.0 equiv) was added to a solution of (±)-**36** (64.8 mg, 0.184 mmol, 1.00 equiv) in MeOH (8 mL) and stirred for 24 h at room temperature. The resulting reaction mixture was diluted with EtOAc (15 mL), then washed with H_2O (15 mL). The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography to afford (±)-**37** as a yellow foam (20 mg, 35%). R_f = 0.35 (50:50 EtOAc/petrol); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.55 (1H, t, *J* = 4.5 Hz), 5.40 (1H, t, *J* = 4.5 Hz), 4.07 (1H, br s), 3.77 (3H, s), 3.71 (1H, s), 3.07 (1H, br s), 2.74 (1H, d, *J* = 6.0 Hz), 1.86 ppm (1H, br s); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 210.0 ($[Fe(CO)_3]$), 173.7, 84.8, 84.5, 81.5, 62.0, 59.1, 53.5 ppm; FTIR (neat): $\tilde{\nu}_{max}$ = 3426, 3361, 2059, 1983, 1708, 1274, 1122, 1014 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{10}O_7Fe$: 332.9673 $[M+Na]^+$; found: 332.9673.

General procedure for de-metallation to give free dienes 38 to 44: A solution of ceric ammonium nitrate (3.00 equiv) in acetone (1 mL) was added dropwise over 5 mins to a solution of the relevant iron complex in wet acetone (2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for an additional time period. Water was added (5 mL) and the solution was extracted with Et_2O (2×20 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography.

*Formation of **38***: In accordance with the general procedure, the reaction of **29** (3.4 mg) for 5 min gave a white solid (2.1 mg, 91%). R_f = 0.35 (20:80 EtOAc/hexane); $[\alpha]_D^{25}$ = +40 (*c* = 0.1 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53–7.50 (2H, m; Ar-H), 7.31–7.30 (3H, m; Ar-H), 7.13 (1H, d, *J* = 5.5 Hz; H-6), 6.28 (1H, dd, *J* = 9.0, 5.5 Hz; H-4), 6.24 (1H, dd, *J* = 9.0, 5.5 Hz; H-5), 6.08 (1H, s; H-3), 4.08 (1H, d, *J* = 5.5 Hz; H-2), 3.77 (3H, s; -$COOCH_3$), 1.98 ppm (3H, s; -$OC(O)CH_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 170.3, 166.2, 135.7, 133.9, 132.2, 129.0, 128.5, 123.8, 123.7, 67.7, 52.2, 46.4, 21.2 ppm; FTIR (neat): $\tilde{\nu}_{max}$ = 2924, 2854, 1743, 1715, 1580, 1439, 1369, 1286, 1228, 1078, 1025, 991, 951, 749, 694 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{16}SO_4$: 327.0667 $[M+Na]^+$; found: 327.0663.

*Formation of (±)-**39***: In accordance with the general procedure, the reaction of (±)-**30** (63.8 mg) for 5 min gave a brown oil (37.1 mg, 85%). R_f = 0.42 (20:80 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.47 (2H, m; Ar-H), 7.28–7.25 (3H, m; Ar-H), 6.36 (1H, d, *J* = 9.5 Hz; H-6), 5.99–5.91 (3H, m; H-3,4,5), 4.04 (1H, d, *J* = 4.5 Hz; H-2), 3.65 (3H, s; -$COOCH_3$), 1.99 ppm (3H, s; -$OC(O)CH_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 169.6, 169.5, 134.8, 131.3, 128.3, 127.0, 125.1, 123.2, 122.9, 79.6, 52.4, 48.6, 20.7 ppm; FTIR (neat): $\tilde{\nu}_{max}$ = 2951, 1742, 1581, 1473, 1438, 1368, 1268, 1229, 1131, 1074, 1012, 986, 951, 909, 752, 717, 691, 651 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{16}SO_4$: 327.0667 $[M+Na]^+$; found: 327.0687.

*Formation of **40**:* In accordance with the general procedure, the reaction of **31** (8.4 mg) for 50 min gave a white solid (3.1 mg, 63%). R_f = 0.35 (20:80 EtOAc/hexane); $[\alpha]_D^{25}$ = +20 (*c* = 0.1 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (1H, d, *J* = 6.0 Hz; H-6), 6.28–6.22 (2H, m; H-4,5), 5.91 (1H, d, *J* = 7.0 Hz; H-2), 3.78 (3H, s; -$COOCH_3$), 2.78 (1H, dd, *J* = 20.0, 3.0 Hz; H-3), 2.58 (1H, dd, *J* = 20.0, 7.0 Hz; H-3), 1.99 ppm (3H, s; -$OC(O)CH_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 170.4, 166.6, 137.2, 133.0, 123.8, 122.7, 62.7, 51.9, 30.7, 21.3 ppm; FTIR (neat): $\tilde{\nu}_{max}$ = 2961, 2923, 2859, 1716, 1658, 1467, 1378, 1261, 1079, 1030, 799 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_{12}O_4$: 219.0633 $[M+Na]^+$; found: 219.0615.

*Formation of **41**:* In accordance with the general procedure, the reaction of **33** (26.4 mg) for 3 h gave a colourless oil (10.5 mg, 63%). R_f = 0.27

(20:80 EtOAc/hexane); $[\alpha]_D^{25} = +840$ ($c = 0.1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.30$ (1H, dd, $J = 6.0$, 0.5 Hz; H-6), 6.52 (1H, dd, $J = 9.5$, 6.0 Hz; H-5), 6.21 (1H, dd, $J = 9.5$, 5.5 Hz; H-4), 5.93 (1H, dd, $J = 2.0$, 1.0 Hz; H-2), 4.00 (1H, dd, $J = 5.5$, 1.5 Hz; H-3), 3.80 (3H, s; -$COOCH_3$), 2.04 ppm (3H, s; -$OC(O)CH_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 170.0$, 165.7, 135.4, 127.6, 126.5, 125.4, 66.1, 56.4, 52.3, 21.1 ppm; FTIR (neat): $\tilde{\nu}_{max} = 2917$, 2850, 1744, 1718, 1438, 1371, 1289, 1259, 1226, 1082, 1022, 757 cm^{-1}; HRMS (ESI): m/z calcd for $C_{10}H_{11}O_4N_3$: 260.0642 $[M+Na]^+$; found: 260.0621.

*Formation of (±)-**42***: In accordance with the general procedure, the reaction of (±)-**34** (77.3 mg) for 4 h gave a white solid (34.9 mg, 64%). $R_f = 0.27$ (10:90 EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.49$ (1H, d, $J = 9.5$ Hz; H-6), 6.37 (1H, dd, $J = 9.5$, 5.5 Hz; H-4), 6.20 (1H, dd, $J = 9.5$, 5.5 Hz; H-5), 5.90 (1H, dd, $J = 9.0$, 5.0 Hz; H-3), 3.86–3.83 (1H, m; H-2), 3.83 (3H, s; -$COOCH_3$), 2.02 ppm (3H, s; -$OC(O)CH_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 169.6$, 169.4, 126.8, 126.6, 124.7, 120.1, 77.3, 57.7, 53.3, 20.7 ppm; FTIR (neat): $\tilde{\nu}_{max} = 2957$, 1744, 1438, 1371, 1272, 1235, 1075, 1021, 937, 852, 808, 746 cm^{-1}; HRMS (ESI): m/z calcd for $C_{10}H_{11}O_4N_3$: 260.0642 $[M+Na]^+$; found: 260.0625.

*Formation of **43***: In accordance with the general procedure, the reaction of **35** (14.7 mg) for 5 min gave a white solid (4.7 mg, 53%). $R_f = 0.19$ (35:65 EtOAc/hexane); $[\alpha]_D^{25} = +400$ ($c = 0.1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.26$–7.25 (1H, m; H-6), 6.29–6.28 (2H, m; H-4,5), 5.89 (1H, d, $J = 2.5$ Hz; H-2), 4.34 (1H, brs; H-3), 3.78 (3H, s; -$COOCH_3$), 2.34 (1H, d, $J = 6.0$ Hz; -OH), 2.07 ppm (3H, s; -$OC(O)CH_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 171.0$, 166.2, 135.2, 133.0, 125.2, 124.2, 70.7, 67.7, 52.2, 21.2 ppm; FTIR (neat): $\tilde{\nu}_{max} = 3444$, 2955, 2922, 2853, 1741, 1714, 1651, 1587, 1438, 1407, 1371, 1230, 1121, 1082, 1020, 992, 960, 917, 876, 815, 743, 682 cm^{-1}; HRMS (ESI): m/z calcd for $C_{10}H_{12}O_5$: 235.0577 $[M+Na]^+$; found: 235.0616; m/z calcd for $C_{10}H_{12}O_5$: 447.1262 $[2M+Na]^+$; found: 447.1278.

*Formation of (±)-**44***: In accordance with the general procedure, the reaction of (±)-**36** (13.8 mg) for 25 min gave a beige solid (8.8 mg, 100%). $R_f = 0.48$ (50:50 EtOAc/petrol); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.33$ (1H, d, $J = 9.5$ Hz; H-6), 6.17 (1H, dd, $J = 9.5$, 5.0 Hz; H-5), 6.09 (1H, dd, $J = 9.5$, 5.0 Hz; H-4), 6.01 (1H, dd, $J = 9.5$, 5.0 Hz; H-3), 4.36 (1H, dd, $J = 8.5$, 4.5 Hz; H-2), 3.80 (3H, s; -$COOCH_3$), 2.05 (3H, s; -$OC(O)CH_3$), 1.94 ppm (1H, d, $J = 9.0$ Hz; OH); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 170.0$, 169.9, 126.6, 126.5, 124.4, 124.3, 79.6, 68.6, 52.9, 20.9 ppm; FTIR (neat): $\tilde{\nu}_{max} = 3452$, 2955, 1985, 1732, 1436, 1412, 1370, 1273, 1232, 1136, 1078, 1047, 1019, 1000, 953, 920, 879, 812, 729, 796, 694 cm^{-1}; HRMS (ESI): m/z calcd for $C_{10}H_{12}O_5$: 235.0577 $[M+Na]^+$; found: 235.0616; m/z calcd for $C_{10}H_{12}O_5$: 447.1262 $[2M+Na]^+$; found: 447.1255.

Acetylation of 43 to give 55: Ac_2O (3.8 μL, 0.040 mmol, 2.0 equiv) was added portionwise to a solution of compound **43** (4 mg, 0.018 mmol, 1.00 equiv) in CH_2Cl_2 (2 mL) at 0°C, and then Et_3N (8.4 μL, 0.060 mmol, 3.2 equiv) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was transferred into a separating funnel and extracted with EtOAc (4×10 mL) and water (10 mL), and the combined organic phases were then dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (30:70 EtOAc/hexane) to give **55** as a white solid (3 mg, 63%). $R_f = 0.35$ (30:70 EtOAc/hexane); $[\alpha]_D^{25} = +440$ ($c = 0.1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.28$ (1H, d, $J = 6.0$ Hz; H-6), 6.37 (1H, dd, $J = 9.5$, 6.0 Hz; H-5), 6.29 (1H, dd, $J = 9.5$, 6.0 Hz; H-4), 5.94 (1H, d, $J = 2.0$ Hz; H-2), 5.29 (1H, dd, $J = 5.0$, 2.0 Hz; H-3), 3.79 (3H, s; -$COOCH_3$), 2.05 ppm (6H, s; 2×-$OC(O)CH_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 169.59$, 169.55, 165.8, 135.1, 129.1, 126.0, 125.4, 67.7, 65.9, 52.1, 20.9, 20.8 ppm; FTIR (neat): $\tilde{\nu}_{max} = 2955$, 1742, 1717, 1594, 1437, 1370, 1295, 1221, 1084, 1022, 967, 749 cm^{-1}; HRMS (ESI): m/z calcd for $C_{12}H_{14}O_6$: 277.0683 $[M+Na]^+$; found: 277.0773; m/z calcd for $C_{12}H_{14}O_6$: 531.1473 $[2M+Na]^+$; found: 531.1581.

Esterification to form 57: A mixture of diol acid **4** (1.03 g, 6.63 mmol, 1.00 equiv) and caesium fluoride (1.51 g, 9.94 mmol, 1.50 equiv) in DMF (15 mL) was stirred at room temperature for 2 min, then ethyl iodide (0.799 mL, 9.94 mmol, 1.50 equiv) was added. The reaction mixture was stirred for 23 h, then diluted with aqueous $NaHCO_3$ (15 mL) and extracted with EtOAc (3×15 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, then purified by chromatography (50:50 EtOAc/hexane) to give **57** as a colourless oil (846 mg, 69%). $R_f = 0.37$ (50:50 EtOAc/petrol); $[\alpha]_D^{25} = -140$ ($c = 0.1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.12$ (1H, dd, $J = 9.5$, 5.5 Hz; H-5), 5.93 (1H, dddd, $J = 9.5$, 5.5, 3.0, 1.0 Hz; H-4), 5.80 (1H, ddt, $J = 9.5$, 2.5, 1.0 Hz; H-3), 5.74 (1H, dd, $J = 9.5$, 1.0 Hz; H-6), 4.83 (1H, d, $J = 5.0$ Hz; H-2), 4.31 (2H, q, $J = 7.0$ Hz; -CH_2CH_3), 3.67 (1H, s; C1-OH), 2.84 (1H, d, $J = 9.5$ Hz; C2-OH), 1.32 ppm (3H, t, $J = 7.0$ Hz; -CH_2CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 175.3$, 132.1, 126.7, 124.9, 122.8, 73.9, 71.0, 63.0, 14.3 ppm; FTIR (neat): $\tilde{\nu}_{max} = 3448$, 3049, 2983, 1727, 1446, 1408, 1369, 1246, 1169, 1078, 1039, 1019, 914, 858, 829, 754, 724, 693, 646 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{12}O_4$: 207.0628 $[M+Na]^+$; found: 207.0748; m/z calcd for $C_9H_{12}O_4$: 391.1364 $[2M+Na]^+$; found: 391.1374.

Complexation to form 58: Nonacarbonyldiiron (3.05 g, 8.28 mmol, 1.5 equiv) was added to ester **57** (1.79 g, 5.52 mmol, 1.0 equiv). THF (200 mL) was added and the reaction mixture was stirred at room temperature for 5 days. The reaction mixture was concentrated under reduced pressure (**caution! toxic pentacarbonyliron distilled over**) and the crude product was purified by chromatography (30:70 EtOAc/petrol) to give **58** as a yellow foam (1.09 g, 61%). $R_f = 0.60$ (30:70 EtOAc/petrol); $[\alpha]_D^{25} = -180$ ($c = 0.1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.38$–5.33 (2H, m; H-4,5), 4.22–4.15 (2H, m; -CH_2CH_3), 3.94 (1H, s; C1-OH), 3.88 (1H, d, $J = 5.0$ Hz; H-2), 3.26 (1H, d, $J = 6.5$ Hz; C2-OH), 3.21 (1H, dt, $J = 6.0$, 2.0 Hz; H-3), 2.82 (1H, dd, $J = 6.0$, 1.5 Hz; H-6), 1.27 ppm (3H, t, $J = 7.0$ Hz; -CH_2CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 210.2$ ([$Fe(CO)_3$]), 174.4, 84.5, 84.2, 77.2, 72.0, 67.6, 64.6, 62.7, 14.0 ppm; FTIR (neat): $\tilde{\nu}_{max} = 3401.5$, 2991, 2905, 2051, 1960, 1720, 1574, 1446, 1377, 1297, 1233, 1175, 1133, 1063, 1026, 936, 866, 831, 737 cm^{-1}; HRMS (ESI): m/z calcd for $C_{12}H_{12}FeO_7$: 346.9825 $[M+Na]^+$; found: 346.9926; m/z calcd for $C_{12}H_{12}FeO_7$: 670.9758 $[2M+Na]^+$; found: 670.9853.

Formation of adducts 59 and (±)-60: Tetrafluoroboric acid diethyl etherate (319 μL, 2.33 mmol 4.00 equiv) was added to a stirred solution of the [η^4] complex **58** (189 mg, 0.583 mmol, 1.00 equiv) in acetic anhydride (5.8 mL) at −10°C and stirred at this temperature for 1 h. Pre-cooled Et_2O (60 mL) was added dropwise to the reaction mixture, giving a light-yellow precipitate. This was filtered by using suction and washed with cold Et_2O (3×5 mL). The crude cation mixture was redissolved in MeCN at 0°C, and $NaBH_4$ (111 mg, 2.91 mmol, 5.00 equiv) was added in one portion. The reaction mixture was allowed to warm to room temperature and was stirred for 18 h, then quenched by addition of H_2O. The product was extracted with CH_2Cl_2 (3×20 mL). The organic layers were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by chromatography (10:90 EtOAc/hexane) to give **59** (10.9 mg, 5%) and (±)-**60** (80.3 mg, 39%) as yellow foams. **59**: $R_f = 0.14$ (10:90 EtOAc/hexane); $[\alpha]_D^{25} = +120$ ($c = 0.1$ in CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.95$ (1H, dd, $J = 4.5$, 1.5 Hz; H-6), 5.52 (1H, t, $J = 5.5$ Hz; H-5), 5.04 (1H, d, $J = 6.5$ Hz; H-2), 4.24–4.02 (2H, m; -CH_2CH_3), 3.22–3.17 (1H, m; H-4), 2.10–2.00 (1H, m; H-3), 2.06 (3H, s; -$OC(O)CH_3$), 1.57 (1H, ddd, $J = 16.0$, 4.5, 1.0 Hz; H-3), 1.24 ppm (3H, t, $J = 7.0$ Hz; -CH_2CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 209.5$ ([$Fe(CO)_3$]), 171.2, 170.1, 90.4, 84.4, 68.5, 68.2, 61.0, 58.6, 34.3, 21.2, 14.1 ppm; FTIR (neat): $\tilde{\nu}_{max} = 2925$, 2057, 1981, 1739, 1710, 1505, 1448, 1368, 1240, 1207, 1098, 1043, 871, 752, 715, 612 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{14}FeO_7 = 372.9974$ $[M+Na]^+$; found: 372.9986. (±)-**60**: R_f 0.25 (10:90 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.47$ (1H, t, $J = 5.5$ Hz; H-4), 5.36 (1H, t, $J = 5.5$ Hz; H-5), 4.18–4.07 (2H, m; -CH_2CH_3), 3.20–3.17 (1H, m; H-3), 3.08 (1H, d, $J = 6.5$ Hz; H-6), 2.73 (1H, d, $J = 16.0$ Hz; H-2), 2.09 (3H, s; -$OC(O)CH_3$), 1.92 (1H, dd, $J = 16.0$, 3.5 Hz; H-2); 1.22 ppm (3H, t, $J = 7.0$ Hz; -CH_2CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 210.6$ ([$Fe(CO)_3$]), 171.3, 170.1, 87.1, 82.3, 81.5, 61.8, 61.6, 60.5, 39.9, 21.0, 14.6 ppm; FTIR (neat): $\tilde{\nu}_{max} = 2985$, 2051, 1969, 1740, 1427, 1370, 1251, 1196, 1097, 1054, 1014, 954, 869 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{14}FeO_7$: 372.9986 $[M+Na]^+$; found: 372.9996.

Deacetoxylation to give cation (±)-61: Iron complex (±)-**60** (51.5 mg, 0.147 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (3 mL) at −12°C and HBF_4–etherate (30.2 μL, 0.220 mmol, 1.50 equiv) was added portionwise.

The reaction mixture was stirred at this temperature for 1 h, then added to cold Et_2O (50 mL) to give a precipitate that was isolated by filtration, washed with Et_2O and dried under vacuum to give (±)-**61** as a pale-yellow powder (55.5 mg, 100%). ^{1}H NMR (300 MHz, CD_3CN): δ = 7.38 (1H, t, J = 5.0 Hz), 6.57 (1H, d, J = 5.5 Hz), 5.91 (1H, t, J = 5.5 Hz), 4.70 (1H, t, J = 6.5 Hz), 4.26 (1H, q, J = 7.0 Hz), 3.27 (1H, dd, J = 15.5, 6.5 Hz), 1.96–1.86 (1H, m), 1.28 ppm (1H, t, J = 7.0 Hz); ^{13}C NMR (75.4 MHz, CD_3CN): δ = 167.6, 105.1, 103.0, 91.3, 71.8, 63.9, 56.0, 24.2, 14.1; HRMS (ESI): m/z calcd for $C_{12}H_{11}FeO_5$: 290.9951 $[M]^+$; found: 290.9925.

Potassium phthalimide as a nucleophile: formation of (±)-62: A suspension of the $[\eta^5]^+$ complex (±)-**61** (78.2 mg, 0.223 mmol, 1.00 equiv) and potassium phthalimide (124 mg, 0.699 mmol, 3.00 equiv) in CH_2Cl_2 (4.4 mL) was cooled to 0°C. Diisopropylethyl amine (42.7 µL, 0.246 mmol, 1.10 equiv) was added dropwise and the reaction mixture was stirred at 0°C for 30 min before being allowed to warm to room temperature. The reaction mixture was stirred at this temperature for 23 h, then quenched by the addition of water, transferred to a separating funnel and extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (15:85 EtOAc/petrol) to give (±)-**62** as a yellow solid (70.8 mg, 73%). R_f = 0.73 (15:85 EtOAc/petrol); m.p. 124–125°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (2H, dd, J = 5.5, 3.0 Hz; Ar-H), 7.69 (2H, dd, J = 5.5, 3.0 Hz; Ar-H), 6.33 (1H, d, J = 4.5 Hz; H-6), 5.59 (1H, t, J = 5.5 Hz; H-5), 4.90 (1H, dt, J = 11.5, 3.5 Hz; H-3), 4.24–4.08 (2H, m; -CH_2CH$_3$), 2.91 (1H, dd, J = 5.0, 3.5 Hz; H-4), 2.78 (1H, dd, J = 15.0, 11.5 Hz; H-2), 1.84 (1H, dd, J = 15.0, 4.0 Hz; H-2), 1.26 ppm (3H, t, J = 7.0 Hz; -CH$_2$CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.6, 167.7, 134.0, 131.7, 123.2, 89.5, 85.7, 60.8, 60.0, 58.2, 48.3, 26.3, 14.1 ppm; FTIR (neat): $\tilde{\nu}_{max}$ = 2982, 2057, 1982, 1774, 1708, 1468, 1382, 1354, 1327, 1270, 1249, 1117, 1083, 1042, 881, 716, 649 cm^{-1}; HRMS (ESI): m/z calcd for $C_{20}H_{15}FeNO_7$: 460.0091 $[M+Na]^+$; found: 460.0104.

De-metallation to form (±)-63: Aqueous hydrogen peroxide (30%, 6.0 mL) was added to a solution of complex (±)-**62** (38 mg, 0.0869 mmol, 1.00 equiv) in EtOH (17 mL) at 0°C, followed by the dropwise addition of aqueous NaOH (1.0 M, 5.2 mL). The reaction mixture was stirred for 5 min, then diluted with brine (saturated, 50 mL) and the product was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give (±)-**63** as a light yellow foam (19.8 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (2H, dd, J = 5.5, 3.0 Hz), 7.74 (2H, dd, J = 5.5, 3.0 Hz), 7.09–7.08 (1H, m), 6.23 (1H, ddd, J = 9.5, 5.5, 3.0 Hz), 6.00 (1H, dd, J = 9.5, 3.0 Hz), 5.23 (1H, ddt, J = 14.5, 10.5, 3.0 Hz), 4.22 (2H, q, J = 7.0 Hz), 2.93 (1H, ddd, J = 17.5, 15.0, 2.5 Hz), 2.81 (1H, dd, J = 17.0, 10.0 Hz), 1.30 ppm (3H, t, J = 7.0 Hz). Data are in agreement with those reported previously.[71]

***tert*-Butyl carbamate as a nucleophile: formation of (±)-64**: Diisopropylethyl amine (38.5 µL, 0.221 mmol, 1.50 equiv) was added dropwise to a suspension of the $[\eta^5]^+$ complex (±)-**61** (51.5 mg, 0.1471 mmol, 1.00 equiv) and *tert*-butyl carbamate (34.5 mg, 0.294 mmol, 2.00 equiv) in CH_2Cl_2 (3 mL) at 0°C. The reaction mixture was stirred for 30 min before being allowed to warm to room temperature. The reaction mixture was stirred at this temperature for 23 h then quenched by the addition of water, transferred to a separating funnel and extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (20:80 EtOAc/petrol) to give (±)-**64** as a yellow oil (48.2 mg, 82%). R_f = 0.59 (20:80 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.20 (1H, d, J = 4.0 Hz), 5.39 (1H, dd, J = 6.0, 4.5 Hz), 4.40–4.17 (2H, m), 4.21–4.03 (2H, m), 3.27 (1H, br s), 2.84 (1H, dd, J = 15.0, 11.0 Hz), 1.41 (9H, s), 1.25 (3H, t, J = 7.0 Hz), 1.16 ppm (1H, dd, J = 15.0, 3.0 Hz). Data are in agreement with those reported previously.[52]

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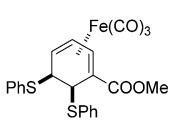
[58] For entries 5 and 6 (Table 1), isolation of the intermediate cations (**21**·PF_6^- and **22**·PF_6^-) by precipitation was not a clean process; in the case of entry 6 (Table 1), byproduct **65** was also obtained in low yield. We tentatively ascribe the formation of **65** to the deacetoxylation of product (±)-**29** by traces of residual acid followed by further nucleophilic attack to incorporate a second equivalent of thiophenolate (i.e., an $[\eta^4]\rightarrow[\eta^5]^+\rightarrow[\eta^4]\rightarrow[\eta^5]^+\rightarrow[\eta^4]$ sequence).



65 [η^4]

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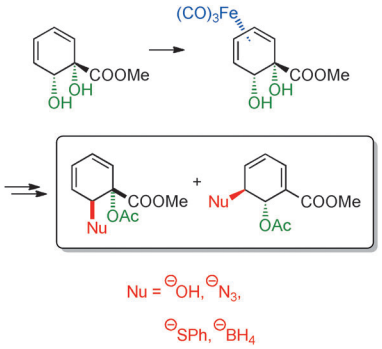
Synthesis Behind the Iron Curtain: Biooxidation of benzoic acid by *Ralstonia eutropha B9* gives an unusual cyclohexadiene diol with a quaternary stereocentre. New iron complexes of this chiron, formed on treatment with acid, provide a versatile library of cyclohexadiene building blocks (see scheme), which have been used in the formal syntheses of oseltamivir.



Microbial Arene Oxidation

*M. Ali Khan, M. F. Mahon, J. P. Lowe, A. J. W. Stewart, S. E. Lewis** ..... ▮▮▮▮–▮▮▮▮

Valuable New Cyclohexadiene Building Blocks from Cationic η^5-Iron–Carbonyl Complexes Derived from a Microbial Arene Oxidation Product