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Reactivity of acyclic (pentadienyl)iron(1+) cations: Synthetic studies directed toward the frondosins

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The spectral data used in the research for this article may be found here.

Reactivity of acyclic (pentadienyl)iron(1+) cations: Synthetic studies directed toward the frondosins†

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A short, 4-step route to the scaffold of frondosin A and B is reported. The [1-methoxycarbonyl-5-(2′,5′-dimethoxyphenyl)pentadienyl]$Fe(CO)_3^+$ cation was prepared in two steps from (methyl 6-oxo-2,4-hexadienoate)$Fe(CO)_3$. Reaction of this cation with isopropenyl Grignard or cyclohexenyllithium reagents affords (2-alkenyl-5-aryl-1-methoxycarbonyl-3-pentene-1,5-diyl)$Fe(CO)_3$ along with other addition products. Oxidative decomplexation of these (pentenediyl)iron complexes, utilizing $CuCl_2$, affords 6-aryl-3-methoxycarbonyl-1,4-cycloheptadienes via the presumed intermediacy of a cis-divinylcyclopropane.

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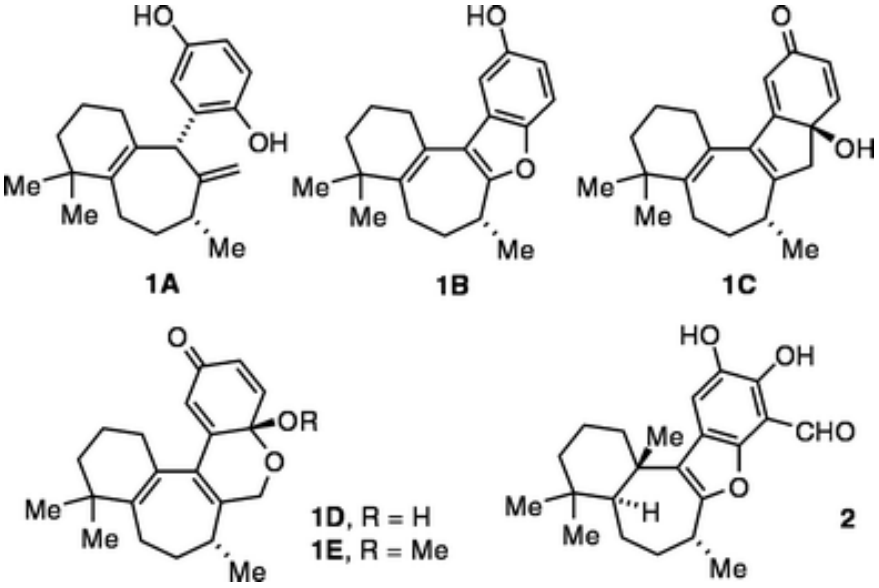
Introduction

The (+)-frondosins A–E (**1A–E**, Fig. 1, Scheme 1) are a family of sesquiterpenes hydroquinone derivatives isolated from the sponge Dysidea frondosa in 1997.[1] These compounds were found to inhibit the binding of interleukin-8 (IL-8) to its receptor in the micromolar range, with **1A** and **1B** being the most active (IC_{50} = 3.4 and 9.6 mM, respectively). Since IL-8 is involved in enlisting neutrophiles to a site of inflammation, inhibitors of IL-8 might be useful in treating autoimmune disorders as well as tumor suppression. Additionally, frondosins A and D of the opposite optical rotation were found in organic extracts of Euryspongia sp which exhibited HIV inhibitory activity.[1b] More recently, liphagal (**2**), a structurally related compound was isolated from the sponge Aka coralliphaga.[2] Liphagal was found to be a selective inhibitor of PI3 kinase α at 100 nM level. In addition to their intriguing biological activity, the structural complexity of **1A–E** and **2** has generated significant synthetic interest.[3,4]



Scheme 1

We have previously reported an iron-mediated route to cycloheptadienes.[5] This route involves the addition of alkenyl Grignard reagents to (1-methoxycarbonylpentadienyl)iron(1+) cations **3** to afford the corresponding neutral (2-alkenyl-3-penten-1,5-diyl)iron complexes **4**. Oxidatively induced reductive elimination of **4** results in the formation of divinylcyclopropanes **5** which undergo Cope

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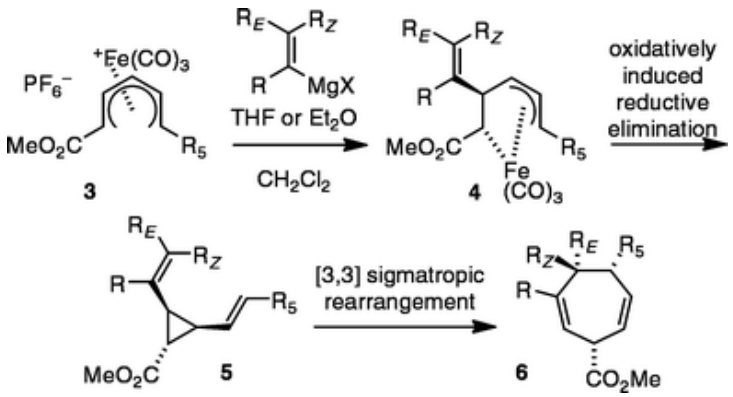
rearrangement to afford 1,4-cycloheptadienes **6**. We have previously utilized this methodology for the preparation of the 5-7-5 fused ring system of the guianolides.[5d] We herein report on synthetic studies directed toward frondosins A and B which utilizes this methodology for the formation of the seven-membered ring (Scheme 2).



Scheme 2

Results and discussion

The reaction of tricarbonyl(methyl 6-oxo-2,4-hexadienoate)iron **7** with the Grignard formed from 1-bromo-2,5-dimethoxybenzene gave (dienol)iron complex **8**, which upon dehydration with HPF_6/acetic anhydride afforded the acyclic (pentadienyl)iron(1+) cation **9a** (Scheme 3). This cation was assigned a cisoid structure on the basis of its ^{1}H NMR spectral data. In particular, the signals for H-2 and H-4 each appear as a doublet of doublets (J = ca. 7 and 11-14 Hz); the larger couplings are consistent with a trans orientation with H-1 and H-5 respectively. The chemical shifts and coupling constants for **9a** are similar to those reported for the (1-methoxycarbonyl-5-phenylpentadienyl)$Fe(CO)_3^+$ cation **9b**.[6]

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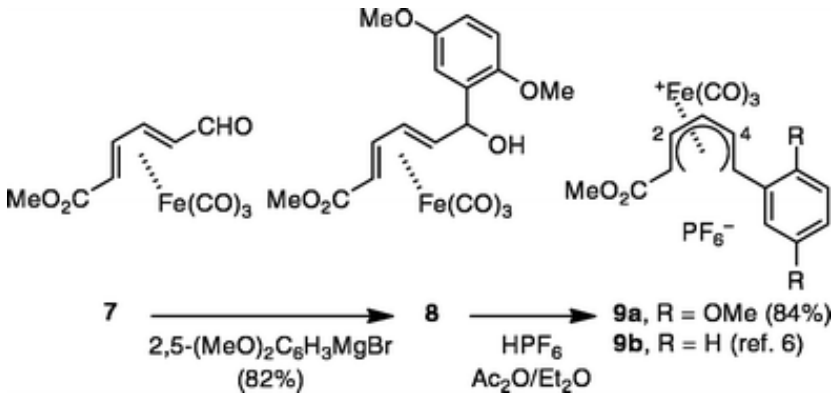

Scheme 3

Reaction of (±)-**9a**, in methylene chloride, with commercially available isopropenylmagnesium bromide in THF, gave a separable mixture of isomeric complexes (±)-**10** and (±)-**11** (Scheme 4). The structures of **10** and **11** were tentatively assigned on the basis of their NMR spectral data; in particular, the three separate signals at δ 200–212, the signal at δ 94–100 and the signal at δ 11–15 ppm in the ^{13}C NMR spectra of each **10** and **11** are characteristic of the three metal carbonyls, the central allyl carbon and the carbon σ-bonded to iron in (3-pentene-1,5-diyl)iron complexes.[6](Pentenediyl)iron complex **10** was tentatively assigned as resulting from nucleophilic attack at C-2 of **9** by comparison of its ^{1}H NMR spectral data with a similar 2-substituted-(5-aryl-1-methoxycarbonylpent-3-ene-1,5-diyl)iron complex produced from **9b**,[6] while **11** was assigned a 4-substituted-(5-aryl-1-methoxycarbonylpent-2-ene-1,5-diyl)iron structure in order to be unique from **10**. These tentative structural assignments were eventually corroborated by single crystal diffraction analysis of each.‡

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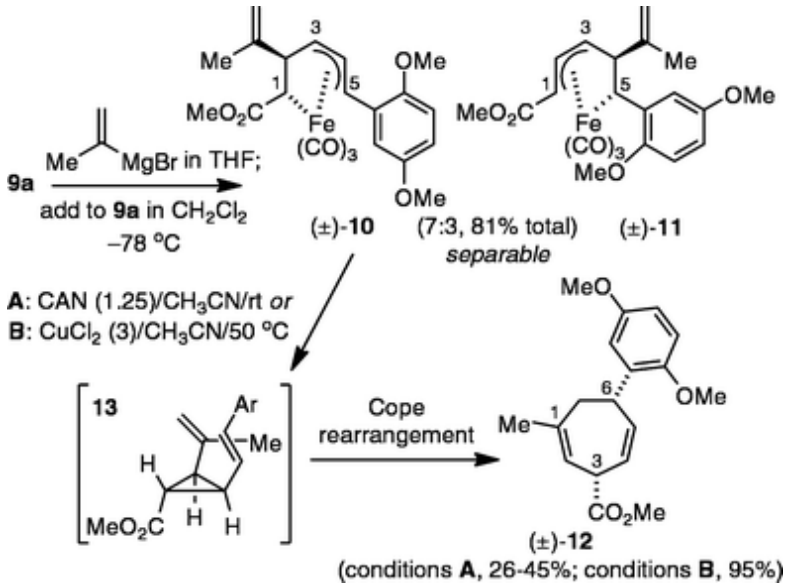

Scheme 4 (Ar = 2,5-dimethoxyphenyl).

Oxidative decomplexation of **10** with cerium ammonium nitrate (CAN) gave the cycloheptadiene (±)-**12** in low and variable yield (conditions **A**, Scheme 4). This reaction presumably proceeds *via* the intermediacy of the *cis*-divinylcyclopropane **13**, which was not observed. The low yield of this product may be due to further oxidation of the *p*-dimethoxybenzene ring with CAN to afford a *p*-quinone substituted product. Oxidative decomplexation of **10** with $CuCl_2$ (conditions **B**, Scheme 4) gave **12** in considerably improved yield (95%). Attempts to use $CuBr_2$, Ag_2O, $Pb(OAc)_4$ or Dess–Martin periodinane for oxidative decomplexation were unsuccessful, giving only unreacted starting material. The structure of **12** was assigned on the basis of its NMR spectral data; in particular signals for the three olefinic protons appear at δ 5.65–5.75 (2H) and 6.04 (1H) ppm, while multiplets at 4.07–4.14 and 4.25–4.31 ppm correspond to H-3 and H-6.

With successful model studies completed, attention was turned to preparing the bicyclo[5.4.0]undecane scaffold of the frondosins. In our hands, attempts to prepare the Grignard reagent from commercially available 1-bromocyclohexene (**14a**) were unsuccessful.[7] For this reason, it was necessary to prepare 1-cyclohexenyllithium by lithium-halogen exchange using *t*-BuLi/pentane. Addition of a solution of this organolithium reagent, *prepared in THF*, to **9a** in CH_2Cl_2

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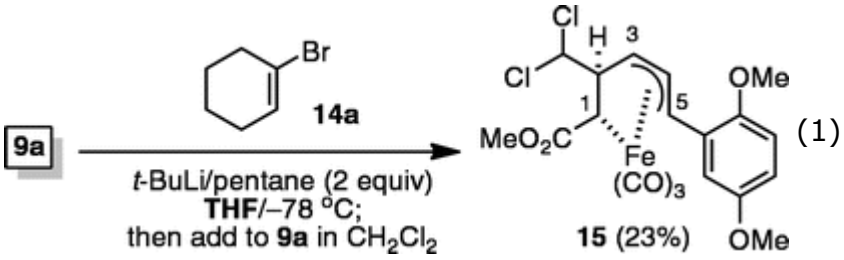
(−78 °C) gave the 2-substituted (pentenediyl)iron complex **15** (eqn (1)). This segment of the structure was assigned by comparison of portions of its NMR spectral data with those for **10**; in particular the chemical shifts for H-1, H-2, H-3, H-4, and H-5 of **15** (δ 0.68, *ca*. 3.7, 4.45, 5.44 and 4.50 ppm) are similar to those for **10**. The exact nature of the substituent at C-2 was initially unclear, however single crystal diffraction analysis‡ revealed this to be a dichloromethyl substituent. Presumably **15** arises via deprotonation of the CH_2Cl_2 solvent, followed by nucleophilic addition of the resultant dichloromethyl anion at C-2.



(1)

In contrast, addition of the organolithium reagent from 1-bromocyclohexene by lithium-halogen exchange, *prepared in ether/pentane*, to **9a** in CH_2Cl_2 (−78 °C) gave a separable mixture of **16a** and **17a** (Scheme 5). Complex **16a** was assigned a (pentenediyl)iron structure by comparison of its NMR spectral data with that for **10**. This assignment was corroborated by single crystal diffraction analysis.‡ The structure of **17a** was assigned on the basis of its NMR spectral data. In particular signals at δ 2.81 (d), 5.24 (dd) and 5.98 (dd, J = 5.3 and 10.5) in the ^{1}H NMR spectrum and signals at δ 80.4 and 88.9 ppm in the ^{13}C NMR spectrum and are characteristic of H-2, H-3, H-4, C-3 and C-4 of (2*E*,4*Z*-hexadienoate)$Fe(CO)_3$ complexes.[6,8] In a similar fashion, addition of the organolithium reagent prepared by lithium-halogen exchange of 6,6-dimethyl-1-iodocyclohexene (**14b**)[9] in ether/pentane, to **9a** in CH_2Cl_2 (−78 °C) gave a separable mixture of **16b** and **17b** (Scheme 5). The structures of **16b** and **17b** were assigned by comparison of their NMR spectral data with those for **16a** and **17a**. The structural assignment for **16b** was corroborated by single crystal diffraction analysis (Fig. 1).

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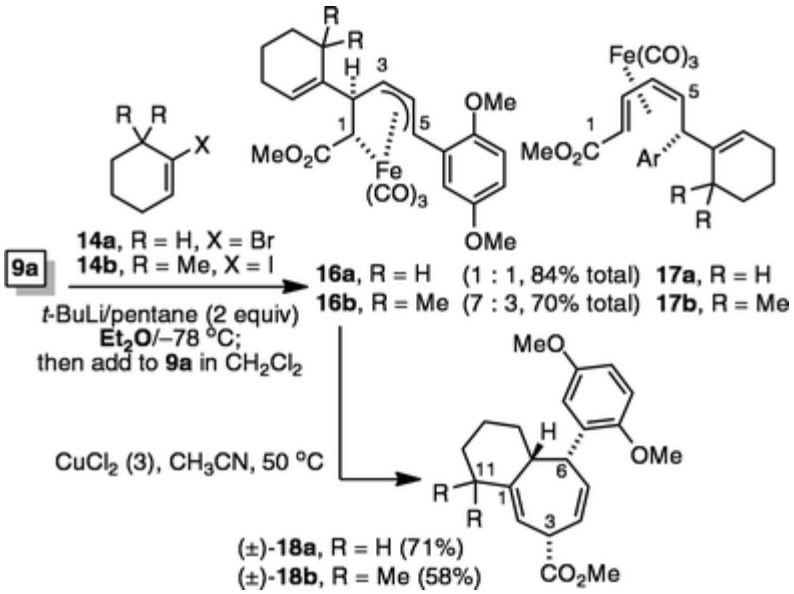

Scheme 5 (Ar = 2,5-dimethoxyphenyl).

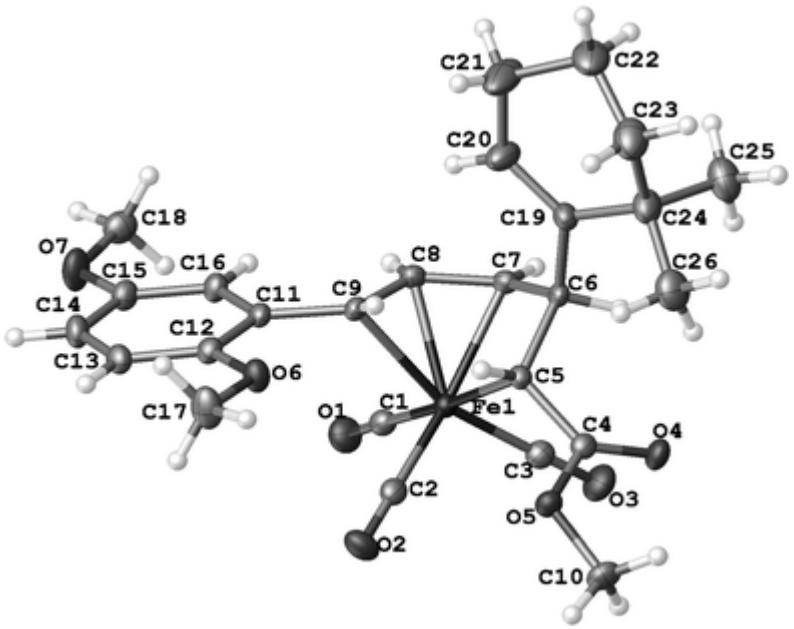

Fig. 1 Molecular structure of (±)-**16b** (arbitrary atom numbering).

The origin of the differences in the reactivity of **9a** with the alkenylmetal species indicated above is presently unclear. However, the results reveal that the regioselectivity of this reaction may depend on such subtle factors as the aggregation of these organometal species.[10]

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Oxidative decomplexation of **16a** or **16b** with $CuCl_2$ gave the bicyclo[5.4.0]undecadiene products (±)-**18a** or (±)-**18b**, respectively. The structures of **18a**/**18b** were assigned by comparison of their NMR spectral data with that for **12**.

Conclusions

A 4-step route from (methyl 6-oxo-2,4-hexadienoate)$Fe(CO)_3$ to the 2-arylbicyclo[5.4.0]undecane scaffold of the frondosins was developed. This route relies on nucleophilic addition of an alkenylmetal species to the acyclic (pentadienyl)iron cation **9a**. The low regioselectivity of this nucleophilic addition remains a challenge in this approach. A modified approach to the requisite (pentenediyl)iron complex **16b**, which addresses this limitation, is under investigation and results will be reported in due course.

Experimental

General methods

All reactions involving moisture or air sensitive reagents were carried out under a nitrogen atmosphere in oven-dried glassware with anhydrous solvents. Purifications by chromatography were carried out using silica gel 60 (40–63 μm). NMR spectra were recorded on either a Varian Mercury+ 300 MHz or a Varian UnityInova 400 MHz instrument. $CDCl_3$ and CD_3NO_2 were purchased from Cambridge Isotope Laboratories. ^{1}H NMR spectra were calibrated to 7.27 ppm for residual $CHCl_3$ or 4.33 ppm for CD_2HNO_2. ^{13}C NMR spectra were calibrated from the central peak at 77.23 ppm for $CDCl_3$ or 60.5 for CD_3NO_2. Coupling constants are reported in Hz. Elemental analyses were obtained from Midwest Microlabs, Ltd., Indianapolis, IN, USA, and high-resolution mass spectra were obtained from the University of Nebraska Center for Mass Spectrometry or the COSMIC lab at Old Dominion University. 1-Bromocyclohexene was purchased from Combi-Blocks, LLC, San Diego, CA, USA. 6,6-Dimethyl-1-iodocyclohexene was prepared from 2,2-dimethylcyclohexanone according to the literature procedure.[9]

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Tricarbonyl[1-methoxycarbonyl-5-(2′,5′-dimethoxy-phenyl)pentadienyl]iron(1+) hexafluorophosphate 9a

To a three necked 300 mL round-bottomed flask, equipped with a dropping funnel, condenser and a stirring bar, were charged Mg turnings (0.54 g, 22 mmol) and freshly distilled dry THF (30 mL) under nitrogen. A solution of 1-bromo-2,5-dimethoxybenzene (4.40 g, 20.3 mmol) in dry THF (10 mL) was added dropwise with vigorous stirring under nitrogen. After addition was complete, the reaction mixture was heated at reflux for 30 min. To a solution of **7** (5.20 g, 18.6 mmol) in dry THF (70 mL), cooled to −40 °C, was added dropwise, over 15 min, the previously prepared Grignard solution. After addition was complete, the cooling bath was removed and the reaction mixture was warmed to room temperature and stirred for 3 h. Water (30 mL) was cautiously added, and the mixture was extracted several times with ethyl acetate. The combined extracts were dried ($MgSO_4$) and concentrated to give a crude compound **8** (6.40 g, 82%). δ_H (300 MHz, $CDCl_3$) 1.04 (1H, d, *J* = 7.8, H-2), 1.80 (1H, t, *J* = 8.1, H-5), 3.01 (1H, d, *J* = 8.1, OH), 3.65 (3H, s, OMe), 3.78 (3H, s, OMe), 3.85 (3H, s, OMe), 4.64 (1H, t, *J* = 7.5, H-6), 5.67 (1H, dd, *J* = 4.8 and 9.0, H-4), 5.82 (1H, dd, *J* = 4.8 and 9.0, H-3), 6.80–6.90 (3H, m, ArH); δ_C (75 MHz, $CDCl_3$) 46.1, 51.8, 55.8, 55.9, 66.6, 73.7, 83.6, 85.7, 111.8, 113.4, 113.6, 132.1, 150.6, 154.0, 172.8 (signal for Fe–CO not observed). This compound was used in the next step without further purification. To an ice cold solution of crude **8** (3.00 g, 7.18 mmol) and acetic anhydride (2.2 mL) in dry ether (10 mL) was added dropwise a cold solution of HPF_6 (60 wt% in H_2O, 2.46 mL, 10.1 mmol) in acetic anhydride (4.5 mL). An orange precipitate developed and the reaction mixture was stirred for 20 min and then added to a large excess of ether. The solid was collected by filtration through a sintered-glass funnel, and the solid was washed several times with dry ether. Recrystallization from CH_2Cl_2/hexanes gave **9a** (3.30 g, 84%) as a bright orange solid (Found: C, 39.24; H, 3.36. Calcd for $C_{18}H_{17}O_7FePF_6$: C, 39.59; H, 3.14.); ν_{max} (KBr)/cm^{-1} 2116, 2081 and 1717; δ_H (300 MHz, CD_3NO_2) 3.14 (1H, d, *J* = 10.8, H-1), 3.81 (3H, s, OMe), 3.92 (3H, s, OMe), 4.01 (3H, s, OMe), 4.78 (1H, d, *J* = 13.5, H-5), 6.70 (1H, dd, *J* = 7.2 and 10.5, H-2), 6.96 (1H, dd, *J* = 7.1 and 13.5, H-4), 7.12–7.26 (4H, m, H-3 and ArH); δ_C (75 MHz, CD_3NO_2) 52.2, 54.3, 54.7, 61.3, 92.5, 95.4, 95.9, 102.6, 111.0, 112.4, 119.6, 120.2,

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152.5, 153.3, 168.1 (the signals for the metal carbonyls were not observed).

Reaction of 9a with isopropenylmagnesium bromide

To a solution of cation **9a** (0.55 g, 1.0 mmol) in dry CH_2Cl_2 (40 mL) in a 100 mL Schlenk flask −78 °C under nitrogen, was slowly added a solution of isopropenylmagnesium bromide (0.5 M solution in THF, 2.2 mL, 1.1 mmol). The reaction mixture was stirred at −78 °C for 1 h, and then slowly warmed to room temperature. Saturated NH_4Cl solution (10 mL) was added and the resulting mixture was extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated to give a mixture of **10** and **11** (71 : 29 by ^1H NMR integration; 0.36 g, 81%) as a yellow solid. The mixture was separated by purification over column chromatography (hexanes-ethyl acetate = 20 : 1 → 4 : 1 gradient). Single crystals of **10** and of **11**, suitable for X-ray diffraction, were obtained by slow evaporation of concentrated CH_2Cl_2/hexanes (1 : 9) solutions at room temperature.

Tricarbonyl[1-methoxycarbonyl-5-(2′,5′-dimethoxy-phenyl)-2-(1-methylethenyl)-3-pentene-1,5-diyl)iron (±)-10. (Found: C, 57.16; H, 5.01. Calcd for $C_{21}H_{22}O_7Fe$: C, 57.03; H, 5.01); mp 136–139 °C; δ_H (400 MHz, $CDCl_3$) 0.78 (1H, d, *J* = 8.9, H-1), 1.56 (3H, s, C=C*Me*), 3.70–3.83 (1H, m, H-2), 3.72 (3H, s, OMe), 3.76 (3H, s, OMe), 3.89 (3H, s, OMe), 4.37 (1H, t, *J* = 7.4, H-3), 4.45 (1H, d, *J* = 12.3, H-5), 4.61 and 4.63 (2H, 2 × s, C=CH_2), 5.46 (1H, dd, *J* = 7.1 and 12.5, H-4), 6.75–6.82 (3H, m, ArH); δ_C (100 MHz, $CDCl_3$) 11.7, 19.6, 45.4, 51.6, 55.9, 56.0, 57.7, 70.2, 94.1, 109.2, 109.5, 111.7, 113.0, 129.1, 147.4, 151.5, 153.7, 181.1, 204.6, 210.2, 210.7.

Tricarbonyl[1-methoxycarbonyl-5-(2′,5′-dimethoxy-phenyl)-4-(1-methylethenyl)-2-pentene-1,5-diyl)iron (±)-11. (Found: C, 57.15; H, 5.08. Calcd for $C_{21}H_{22}O_7Fe$: C, 57.03; H, 5.01); mp 117–118 °C; ν_{max} (KBr)/cm^{-1} 2057, 1986 and 1707; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, C=C*Me*), 1.77 (1H, d, *J* = 10.6, H-5), 3.23 (1H, d, *J* = 10.6, H-1), 3.51 (1H, t, *J* = 7.5, H-4), 3.75–3.85 (1H, m, H-3), 3.78 (3H, s, OMe), 3.79 (3H, s, OMe), 3.85 (3H, s, OMe), 4.59 (2H, s, C=CH_2), 5.44 (1H, dd, *J* = 7.8 and 10.2, H-2), 6.61 (1H, dd, *J* = 1.6 and 8.6, ArH), 6.69 (1H, d, *J* = 8.6, ArH), 6.94 (1H, d, *J* = 1.6, ArH); δ_C (100 MHz, $CDCl_3$) 15.0, 20.0, 48.5, 52.1, 55.3, 55.9, 59.9, 62.0, 100.6, 109.2, 109.3, 110.3, 111.1, 139.0, 148.3, 151.3, 153.5, 173.9, 200.6, 210.4, 212.4.

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Tricarbonyl[2-dichloromethyl-1-methoxycarbonyl-5-(2',5'-dimethoxyphenyl)-3-pentene-1,5-diyl)iron (±)-15. To a stirring solution of 1-bromo-1-cyclohexene (0.10 g, 0.62 mmol) in dry THF (5 mL) at −78 °C, in a 50 mL Schlenk flask, was added dropwise a solution of *t*-BuLi (1.7 M in pentane, 0.74 mL, 1.26 mmol). After addition was complete, the mixture was stirred at −78 °C for 1 h, and then the anion solution was transferred by cannula into a stirring solution of cation **9a** (0.15 g, 0.27 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C. To ensure complete transfer of the solution, a further portion of dry THF (1 mL) was transferred by cannula from the flask used for anion preparation. The reaction mixture was stirred for 30 min at −78 °C, then slowly warmed to 0 °C for 4 h, and finally quenched with water (10 mL). The resulting mixture was extracted several times with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (hexanes-ethyl acetate = 20 : 1 → 4 : 1 gradient) to afford (±)-**15** (30 mg, 23%) as a pale yellow solid. Single crystals suitable for X-ray diffraction were obtained from layering in hexanes over a concentrated solution in CH_2Cl_2. (Found: C, 47.09; H, 3.99. Calcd for $C_{19}H_{21}Cl_2O_7Fe$: C, 46.75; H, 4.34); mp 163–166 °C (dec.); ν_{max} (KBr)/cm^{-1} 2066, 1995 and 1688; δ_H (400 MHz, $CDCl_3$) 0.68 (1H, d, *J* = 8.8, H-1), 3.73 (3H, s, OMe), 3.75–3.80 (1H, m, H-2), 3.76 (3H, s, OMe), 3.92 (3H, s, OMe), 4.45 (1H, t, *J* = 7.2, H-3), 4.50 (1H, d, *J* = 12.9, H-5), 4.94 (1H, d, *J* = 10.0, -$CHCl_2$), 5.44 (1H, dd, *J* = 7.2 and 12.8, H-4), 6.83 (1H, d, *J* = 2.6, ArH), 6.84 (1H, s, ArH), 6.87 (1H, d, *J* = 2.4, ArH); δ_C (100 MHz, $CDCl_3$) 13.0, 50.3, 51.8, 54.9, 55.91, 55.94, 70.8, 75.8, 93.6, 109.3, 111.6, 113.6, 128.0, 151.3, 153.8, 179.5, 203.8, 209.2, 209.4.

Reaction of 9a with cyclohexenyllithium in ether

To a stirring solution of 1-bromo-1-cyclohexene (174 mg, 1.08 mmol) in dry Et_2O/dry pentane (2 : 3, 1 mL) at −78 °C, was added dropwise a solution of *t*-BuLi (1.7 M in pentane, 1.28 mL, 2.2 mmol). After addition was complete, the mixture was stirred at −78 °C for 1 h, and then the solution was transferred by cannula into a stirring solution of cation **9a** (300 mg, 0.549 mmol) in dry CH_2Cl_2 (40 mL) at −78 °C. To ensure complete transfer of the solution, a further portion of dry Et_2O/dry pentane (1 mL) was transferred by cannula from the

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flask used for anion preparation. The reaction mixture was stirred for 30 min at −78 °C, then slowly warmed to room temperature over a 3 h period, and finally quenched with water (10 mL). The resulting mixture was extracted several times with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated to give a mixture of **16a** and **17a** (50 : 50 by ^1H NMR integration; 222 mg, 84%) as a sticky yellow solid. The mixture was separated by column chromatography (hexanes-ethyl acetate = 20 : 1 → 4 : 1 gradient). Crystals of **16a** suitable for X-ray diffraction were obtained by slow evaporation from a concentrated CH_2Cl_2/hexanes (1 : 9) solution at room temperature.

Tricarbonyl[2-(1′-cyclohexenyl)-1-methoxycarbonyl-5-(2′,5′-dimethoxy-phenyl)-3-pentene-1,5-diyl)iron (±)-16a. (Found: C, 59.53; H, 5.67. Calcd for $C_{24}H_{26}O_7Fe$: C, 59.77; H, 5.43); mp 147–150 °C (dec.); ν_{max} (KBr)/cm^{-1} 2058, 1989 and 1682; δ_H (400 MHz, $CDCl_3$) 0.76 (1H, d, *J* = 9.1, H-1), 1.40–1.64 (4H, m), 1.74–1.81 (2H, m), 1.86–1.95 (2H, m), 3.68 (1H, t, *J* = 8.3, H-2), 3.71 (3H, s, OMe), 3.76 (3H, s, OMe), 3.90 (3H, s, OMe), 4.33 (1H, t, *J* = 7.4, H-3), 4.44 (1H, d, *J* = 12.2, H-5), 5.27 (1H, br s, C=CH), 5.44 (1H, dd, *J* = 7.0 and 12.4, H-4), 6.76–6.91 (3H, m, ArH); δ_C (100 MHz, $CDCl_3$) 12.4, 22.6, 22.7, 25.1, 25.6, 45.5, 51.5, 55.9, 56.0, 58.4, 70.0, 94.4, 109.5, 111.7, 112.9, 120.0, 129.4, 139.9, 151.5, 153.7, 181.3, 204.6, 210.3, 210.8.

Tricarbonyl[methyl 5-(1′-cyclohexenyl)-5-(2′,5′-dimeth-oxyphenyl)-2E,4Z-pentadienoate]iron (±)-17a. ν_{max} (KBr)/cm^{-1} 2044, 1973 and 1736; δ_H (400 MHz, $CDCl_3$) 1.48–1.64 and 1.84–2.02 (8H, m), 2.81 (1H, d, *J* = 11.5, H-2), 2.97 (1H, dd, *J* = 8.1 and 11.5, H-5), 3.60 (1H, d, *J* = 10.4, H-6), 3.75 (3H, s, OMe), 3.79 (3H, s, OMe), 3.85 (3H, s, OMe), 5.24 (1H, dd, *J* = 5.5 and 7.7, H-4), 5.54 (1H, br s, C=CH), 5.98 (1H, dd, *J* = 5.3 and 10.5, H-3), 6.68–6.80 (3H, m, ArH); δ_C (100 MHz, $CDCl_3$) 22.2, 22.9, 25.4, 26.8, 51.8, 51.9, 54.5, 55.9, 56.0, 57.9, 80.4, 88.9, 110.4, 111.4, 112.2, 124.0, 129.8, 137.9, 151.0, 153.6, 173.2, 210.8; ESI-HRMS calcd for $C_{24}H_{26}O_7FeNa$ ($M+Na^+$): m/z 505.0926, found: m/z 505.0924.

Reaction of 9a with dimethylcyclohexenyllithium

To a stirring solution of 1-iodo-6,6-dimethylcyclohex-1-ene (310 mg, 1.31 mmol) in a solution of dry Et_2O/dry pentane (2 : 3, 1 mL) at

−78 °C in a 50 mL Schlenk flask, was added dropwise a solution of *t*-BuLi (1.7 M in pentane, 1.55 mL, 2.6 mmol). After addition was complete, the mixture was stirred at −78 °C for 1 h, and then the solution was transferred by cannula into a stirring solution of cation **9a** (360 mg, 0.659 mmol) in dry CH_2Cl_2 (40 mL) at −78 °C. To ensure complete transfer of the solution, a further portion of dry Et_2O/dry pentane (1 mL) was transferred by cannula from the flask used for anion preparation. The reaction mixture was stirred for 30 min at −78 °C, then slowly warmed to room temperature over a 3 h period, and finally quenched with water (10 mL). The resulting mixture was extracted several times with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated to give a mixture of **16b** and **17b** (69 : 31 by ^{1}H NMR integration; 235 mg, 70%) as a sticky yellow solid. The mixture was separated by column chromatography (hexanes-ethyl acetate = 20 : 1 → 4 : 1 gradient). Crystals of **16b** suitable for X-ray diffraction were obtained by slow evaporation of a concentrated CH_2Cl_2/hexanes (1 : 9) solution at room temperature.

Tricarbonyl[1-methoxycarbonyl-5-(2′,5′-dimethoxy-phenyl)-2-(6′,6′-dimethylcyclohex-1′-enyl)-3-pentene-1,5-diyl)iron (±)-16b. (Found: C, 61.67; H, 6.19. Calcd for $C_{26}H_{30}O_7Fe$: C, 61.19; H, 5.92.); mp 150–152 °C (dec.); ν_{max} (KBr)/cm^{-1} 2056, 2000, and 1691; δ_H (400 MHz, $CDCl_3$) 0.88 (1H, d, *J* = 9.2, H-1), 0.96 (3H, s, Me), 1.10 (3H, s, Me), 1.47–1.51 (2H, m), 1.33–1.37 (2H, m), 1.89–1.93 (2H, m), 3.71 (3H, s, OMe), 3.76 (3H, s, OMe), 3.86 (1H, t, *J* = 8.6, H-2), 3.90 (3H, s, OMe), 4.36 (1H, t, *J* = 7.5, H-3), 4.57 (1H, d, *J* = 12.5, H-5), 5.26 (1H, t, *J* = 3.5, C=CH), 5.37 (1H, dd, *J* = 7.2 and 12.3, H-4), 6.76–6.90 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 16.3, 19.0, 26.3, 28.4, 29.5, 34.0, 40.8, 41.6, 51.5, 56.0, 56.1, 61.2, 69.4, 93.5, 109.5, 111.7, 112.9, 123.7, 129.6, 148.2, 151.5, 153.8, 180.7, 204.8, 210.5, 210.8. ESI-HRMS calcd for $C_{26}H_{30}O_7FeNa$ (M+Na$^+$): *m/z* 533.1239. Found: *m/z* 533.1232.

Tricarbonyl[methyl 5-(2′,5′-dimethoxyphenyl)-5-(6′,6′-dimethylcyclohex-1′-enyl)-2E,4Z-pentadienoate]iron (±)-17b. ν_{max} (KBr)/cm^{-1} 2042, 1991, 1958 and 1720; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, s, Me), 0.95 (3H, s, Me), 1.38–1.60 (4H, m), 1.98–2.04 (2H, m), 2.94–3.05 (2H, m), 3.75 (3H, s, OMe), 3.76 (3H, s, OMe), 3.86 (3H, s, OMe), 3.87 (1H, d, *J* = 10.7, H-6), 5.19 (1H, dd, *J* = 5.5 and 7.2, H-4), 5.92–5.98 (2H, m, H-3 and C=CH), 6.68–6.80 (3H, m, ArH); δ_C (100 MHz, $CDCl_3$) δ 19.1, 26.5, 28.1, 28.4, 35.6, 40.0, 42.7,

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51.9, 53.5, 56.0, 56.2, 62.7, 80.1, 89.1, 110.4, 111.8, 112.3, 125.8, 130.0, 146.0, 151.1, 153.7, 174.3, 210.8; ESI-HRMS calcd for $C_{26}H_{30}O_7FeNa$ ($M+Na^+$): *m/z* 533.1239. Found: *m/z* 533.1219.

3-Methoxycarbonyl-7-(2′,5′-dimethoxyphenyl)-1-methyl-1,4-cycloheptadiene (±)-12. To a stirring solution of complex **10** (100 mg, 0.226 mmol) in CH_3CN (3 mL) at room temperature, was slowly added a solution of $CuCl_2$ (91 mg, 0.68 mmol) in CH_3CN (10 mL). The solution was stirred at room temperature for 30 min and then warmed to 50 °C with stirring for 1 h. After cooling to room temperature, the solution was concentrated and the residue was taken up in CH_2Cl_2 and charged onto a silica gel column. Purification by column chromatography (hexanes-ethyl acetate = 20 : 1 → 10 : 1 gradient) gave (±)-**12** (65 mg, 95%) as a colorless oil. δ_H (300 MHz, $CDCl_3$) 1.41 (3H, t, *J* = 1.8, Me), 2.37 (1H, dd, *J* = 7.5 and 14.5, H-7), 2.64 (1H, dd, *J* = 3.9 and 14.5, H-7′), 3.76 (3H, s, OMe), 3.77 (3H, s, OMe), 3.81 (3H, s, OMe), 4.07–4.14 (1H, m), 4.25–4.31 (1H, m), 5.65–5.75 (2H, m), 6.04 (1H, dddd, *J* = 1.2, 2.1, 3.9 and 11.4), 6.72 (1H, dd, *J* = 3.3 and 8.7, ArH), 6.79 (1H, d, *J* = 8.7, ArH), 6.82 (1H, d, *J* = 3.3, ArH); δ_C (75 MHz, $CDCl_3$) 26.1, 35.1, 36.7, 43.5, 52.4, 55.9, 56.2, 111.3, 111.5, 115.8, 122.3, 127.3, 133.6, 134.2, 139.1, 151.0, 153.7, 174.5; FAB-HRMS calcd for $C_{18}H_{22}O_4$ (M^+) 302.1518, found 302.1526.

3-Methoxycarbonyl-6-(2′,5′-dimethoxyphenyl)-bicyclo[5.4.0]undeca-1,4-diene (±)-18a. The decomplexation of **16a** (100 mg, 0.207 mmol) with $CuCl_2$ (84 mg, 0.63 mmol) was carried out in a fashion similar to the decomplexation of **10**. Purification of the residue by column chromatography (SiO_2, hexanes-ethyl acetate = 20 : 1 → 10 : 1 gradient) gave (±)-**18a** (50 mg, 71%) a pale ivory solid product; δ_H (400 MHz, $CDCl_3$) 1.10–1.30 (3H, m), 1.58–1.72 (3H, m), 1.91–2.01 (1H, m), 2.06–2.12 (1H, m), 2.18–2.26 (1H, m), 3.77 (3H, s, OMe), 3.78 (3H, s, OMe), 3.79 (3H, s, OMe), 4.42–4.48 (1H, m), 4.68–4.72 (1H, m), 5.64 (1H, br s, H-2), 6.05–6.11 (1H, m, H-3), 6.18 (1H, dd, *J* = 4.2 and 10.2, H-4), 6.72 (1H, dd, *J* = 3.0 and 8.9, ArH), 6.80 (1H, d, *J* = 8.9, ArH), 6.94 (1H, d, *J* = 3.0, ArH); δ_C (100 MHz, $CDCl_3$) 26.2, 28.0, 28.9, 38.2, 39.7, 42.5, 44.6, 52.4, 55.9, 56.1, 110.7, 111.4, 116.2, 116.6, 130.0, 131.7, 132.1, 145.8, 151.4, 153.2, 174.9; ESI-HRMS calcd for $C_{21}H_{26}O_4Na^+$ ($M+Na^+$): *m/z* 365.1723. Found: *m/z* 365.1728.

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3-Methoxycarbonyl-6-(2′,5′-dimethoxyphenyl)-11,11-dimethylbicyclo[5.4.0]undeca-1,4-diene (±)-18b. The decomplexation **16b** (100 mg, 0.207 mmol) with $CuCl_2$ (79 mg, 0.58 mmol) was carried out in a fashion similar to the decomplexation of **10**. Purification of the residue by column chromatography (SiO_2, hexanes-ethyl acetate = 20 : 1 → 10 : 1 gradient) gave (±)-**18b** (42 mg, 58%) as a pale ivory solid; ν_{max}(neat)/cm^{-1} 1734; δ_H (400 MHz, $CDCl_3$) 1.06 (3H, s, Me), 1.08 (3H, s, Me), 1.14–1.28 (2H, m), 1.34–1.50 (3H, m), 1.59–1.66 (1H, m), 2.45 (1H, qd, *J* = 3.2 and 12.8, H-7), 3.792 (3H, s, OMe), 3.796 (3H, s, OMe), 3.80 (3H, s, OMe), 4.49 (1H, q, *J* = 3.2, H-3), 4.69 (1H, t, *J* = 4.0, H-6), 5.67 (1H, d, *J* = 2.0, H-2), 6.18–6.21 (2H, m, H-4 and H-5), 6.74 (1H, dd, *J* = 2.8 and 8.8, ArH), 6.82 (1H, d, *J* = 8.8, ArH), 6.98 (1H, d, *J* = 2.8, ArH); δ_C (100 MHz, $CDCl_3$) 22.7, 26.1, 28.5, 30.2, 38.3, 39.2, 40.1, 42.5, 42.9, 52.4, 55.9, 56.1, 110.5, 111.5, 114.0, 116.3, 129.9, 131.5, 132.3, 151.4, 152.1, 153.2, 175.3. ESI-HRMS Calc. for $C_{23}H_{30}O_4$ ($M+Na^+$): *m/z* 393.2042. Found: *m/z* 393.2026.

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Footnotes

† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of new compounds and ORTEPs for **10, 11, 15** and **16a**. CCDC

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‡ The cif files for **10, 11, 15, 16a** and **16b** have been deposited with the CCDC. **10**: CCDC # 823813; **11**: CCDC # 823815; **15**: CCDC # 823811; **16a**: CCDC # 823812; **16b**: CCDC # 823814. Crystal structure data for compound (±)-**16b**: $C_{26}H_{30}O_7Fe$; M = 510.35; triclinic, $P\bar{1}$; a = 10.2155(4), b = 10.6315(4), c = 13.0110(5) Å, α = 102.007(3)°, β = 106.062(3)°, γ = 110.218(3)°; U = 1199.83(8) $Å^3$; T = 100 K; Z = 2; 18938 reflections measured, 5984 unique (R_{int} = 0.0366). The final wR^2 was 0.1155 (all data).