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Recent Applications of Acyclic (Diene)iron Complexes and (Dienyl)iron Cations in Organic Synthesis

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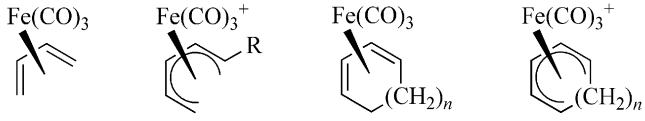
Complexation of (tricarbonyl)iron to an acyclic diene serves to protect the ligand against oxidation, reduction, and cycloaddition reactions, whereas the steric bulk of this adjunct serves to direct the approaches of reagents to unsaturated groups attached to the diene onto the face opposite to iron. Furthermore, the $Fe(CO)_3$ moiety can serve to stabilize carbocation centers adjacent to the diene (i.e. pentadienyliron cations). Recent applications of these reactivities to the synthesis of polyene-, cyclopropane-, cycloheptadiene-, and cyclohexenone-containing natural products or analogues are presented.

Introduction

Although Reihlen and co-workers were the first to prepare an acyclic (butadiene)(tricarbonyl)iron (**1**, Figure 1), in 1930,[1a] the structure of this compound was not proposed until 1958 by Hallam and Pauson, who were also the first to note that complexation of butadiene to iron protected the ligand against catalytic reduction and cycloaddition reactions.[1b] Their structural assignment was eventually corroborated by X-ray crystallography in 1963.[1c] At about the same time, acyclic (pentadienyl)iron(1+) cations (**2**) were first reported by Pettit and co-workers.[2] Complexes of these types, as well as the corresponding cyclic counterparts (**3**, **4**), have found great utility in the synthesis of natural products. Numerous reviews concerning the use of complexes of type **3** and **4** have appeared.[3] Similarly, reviews on the chemistry of complexes of type **1** and **2** covering up to 1999 have appeared.[4] For this reason this review focuses on chemistry relating to complexes **1** and **2** from 2000 onwards.



1 **2** **3** (n = 1,2) **4** (n = 1,2)

Figure 1. Structures of diene- and dienyl-iron complexes.

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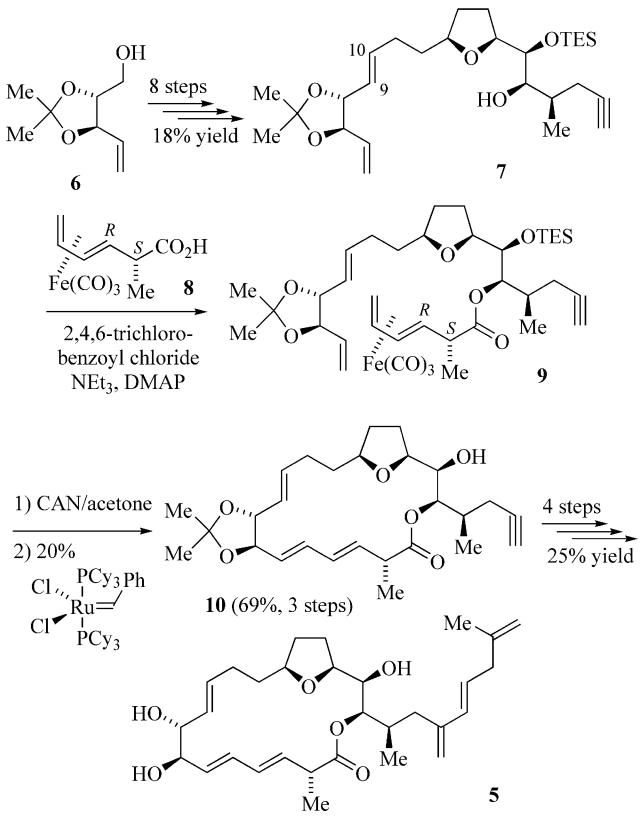
William Donaldson was born near Philadelphia, Pennsylvania. He received his B.A. degree in Chemistry from Wesleyan University (1977), and his Ph.D. in Organometallic Chemistry from Dartmouth College (1981) working with Prof. Russell Hughes, before conducting postdoctoral research with Prof. Myron Rosenblum at Brandeis University (1981–1982). Following a one-year position at Wesleyan University, he joined the faculty at Marquette University in 1983. His research has focused on the application of organoiron complexes to organic synthesis, as well as the synthesis of hydropyran natural products.

Subhabrata Chaudhury is a Bengali from the southern part of Bengal. After receiving his B.Sc. from the University of Calcutta (1997) and M.Sc. degree from the Indian Institute of Technology, Kharagpur (1999), he joined the group of Professor Donaldson at Marquette University where he worked on the development of organoiron methodologies for the total synthesis of natural products. He obtained his Ph.D. degree in 2006 and worked as a postdoctoral fellow in the Department of Medicinal Chemistry at the University of Kansas. Before he started his second period of postdoctoral research at the Department of Biophysics, Medical College of Wisconsin, he returned to Marquette and spent an interim period at Prof. Donaldson's laboratory. In September 2008 he moved to Scotland to join the group of Professor J. S. Clark at the University of Glasgow as a research associate. His research interests involve developing methodologies for the preparation of organic building blocks through the use of transition metal complexes and their application in organic synthesis.

Use of $Fe(CO)_3$ as a Protecting and Stereodirecting Group

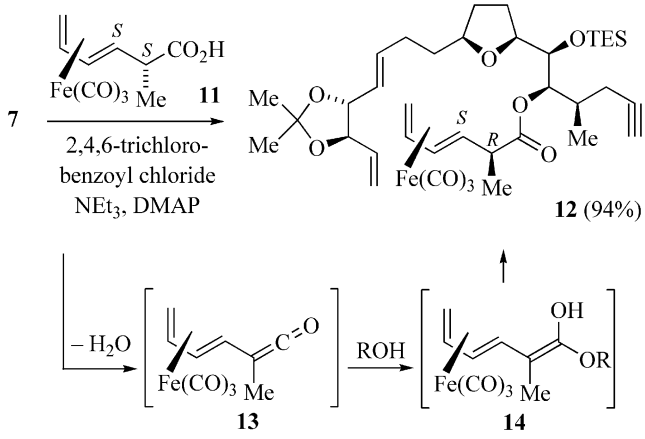
Synthesis of Amphidinolide E

Amphidinolide E (**5**, Scheme 1) is a member of a family of macrolides isolated from the *Amphidinium* species of dinoflagellates.[5] Va and Roush have recently reported a synthesis of **5** that utilized $Fe(CO)_3$ to protect a hexa-3,5-dienoic acid against conjugation.[6] The synthesis begins with conversion of the protected pent-4-ene-1,2,3-triol **6** into the tetrahydrofuranyl alcohol **7** in eight steps. Key steps in this sequence included a Johnson orthoester Claisen rearrangement to form the C9–C10 olefin and a [3+2] annulation[7] with an allylsilane to form the *cis*-tetrahydrofuranyl ring. Attempts to esterify **7** with 2-methylhexa-3,5-dienoic acid were unsuccessful and generally led to recovery of **7** and the *conjugated* diene 2-methylhexa-2,4-dienoic acid. Alternatively, esterification of [(2*S*,3*R*)-2-methylhexa-3,5-dienoic acid]$Fe(CO)_3$[8] (**8**) with **7** cleanly gave **9**. In this case, iron serves as a protecting group such that the diene does not undergo isomerization. Oxidative decomplexation of **9**, followed by ring-closing metathesis[9] in the presence of the first-generation Grubbs catalyst, afforded the macrolide ring **10** exclusively as the (3*E*,5*E*,9*E*) stereoisomer. Completion of the synthesis involved hydrostanyllation of the alkyne, conversion into the 2-alkenyl iodide, cleavage of the protecting groups, and Pd-catalyzed coupling.



Scheme 1. Synthesis of amphidinolide E.

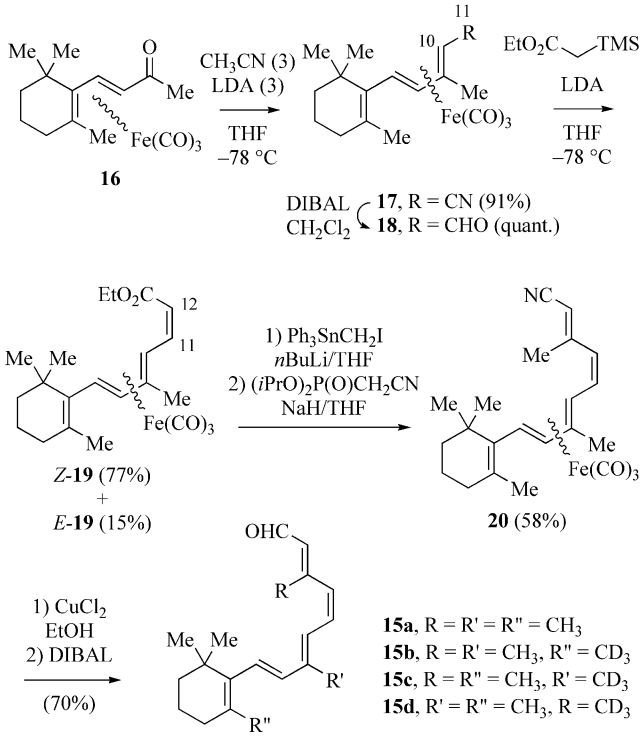
During the course of this work, Va and Roush discovered that the esterification of the diastereomeric [(2*S*,3*S*)-2-methylhexa-3,5-dienoic acid]$Fe(CO)_3$ (**11**) with **7** proceeded with complete inversion of the C2-methyl bond to afford **12** (Scheme 2).[10] These authors propose that the esterification of **11** proceeds through dehydration to generate the ketene intermediate **13**; addition of the alcohol then generates the ketene hemiacetal **14**. Protonation of **14** occurs through the *s-trans* conformer and on the face opposite to the sterically bulky $Fe(CO)_3$ group. Notably, the *relative* configurations at C2 and C3 of **9** and **12** are the same (i.e., 2*S*,3*R* compared to 2*R*,3*S*), and so it is likely that the transformation of **8** into **9** proceeds through the enantiomeric ketene (*ent*-**13**).



Scheme 2. Esterification of (2*S*,3*S*)-(2-methylhexa-3,5-dienoic acid)$Fe(CO)_3$.

Stereoselective Synthesis of (11*Z*)-Retinal

Ito and co-workers have reported a highly stereoselective synthesis of (11*Z*)-retinal (**15a**, Scheme 3), the chromophore of the visual pigment rhodopsin, which utilizes $Fe(CO)_3$ complexation to facilitate generation of the (11*Z*)-olefin.[11a,11b] The synthesis begins with a nitrile aldol reaction between (β-ionone)$Fe(CO)_3$ (**16**) and acetonitrile. This reaction proceeds with migration of the iron fragment to give **17**. 1,3-Migration of the tricarbonyliron group has previously been observed.[4g,12] The presence of a terminal electron-withdrawing substituent (e.g. –CN) and the use of excess nucleophile generally leads to the more thermodynamically stable (diene)iron complex. Reduction of **17** gives the trienal **18**, which upon Peterson olefination with ethyl trimethylsilylacetate affords a separable mixture of (*Z*)- and (*E*)-**19** (77:15). Notably, Wittig or Horner–Emmons olefination of **18** gave only the *E* stereoisomer. Conversion of (*Z*)-**19** into nitrile **20**, followed by decomplexation and nitrile reduction, gave **15a**. Nakanishi's group has recently used this route to prepare the isotopically labeled (11*Z*)-retinals **15b–d**; examination of the labeled retinals by solid-state ^2H NMR spectroscopy provided information on the orientations of these molecules in the rhodopsin binding pocket.[11c]



Scheme 3. Stereoselective synthesis of (11*Z*)-retinal by organoiron chemistry.

The explanation of the *Z*-selective Peterson olefination is based on the approach of the anion of trimethylsilylacetate towards **18** as its *s-trans* conformer (about the C10–C11 bond) on the face opposite to the sterically bulky (tricarbonyl)iron moiety. Of the two synclinal transition states of lowest presumed energy, **TS-1** and **TS-2** (Figure 2), only **TS-1** avoids steric repulsions between the bulky TMS group and the (diene)$Fe(CO)_3$ group. A *syn* elimination from the resulting β-silyl alcohol,[13] as is known for anionic conditions, results preferentially in the (11*Z*) stereoisomer.

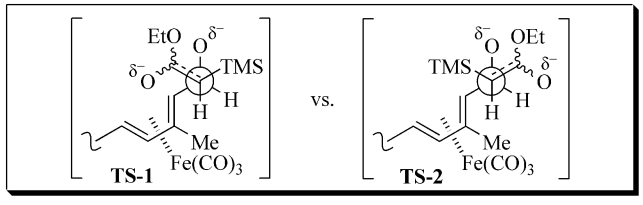
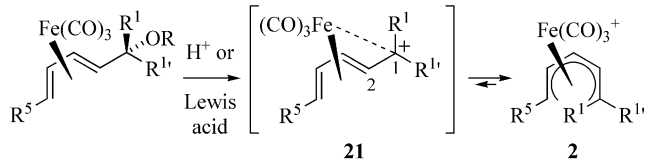


Figure 2. Explanation for *Z*-selective Peterson olefination of **18**.

Reactivity of *transoid* (Pentadienyl)iron(1+) Cations Generated in Situ

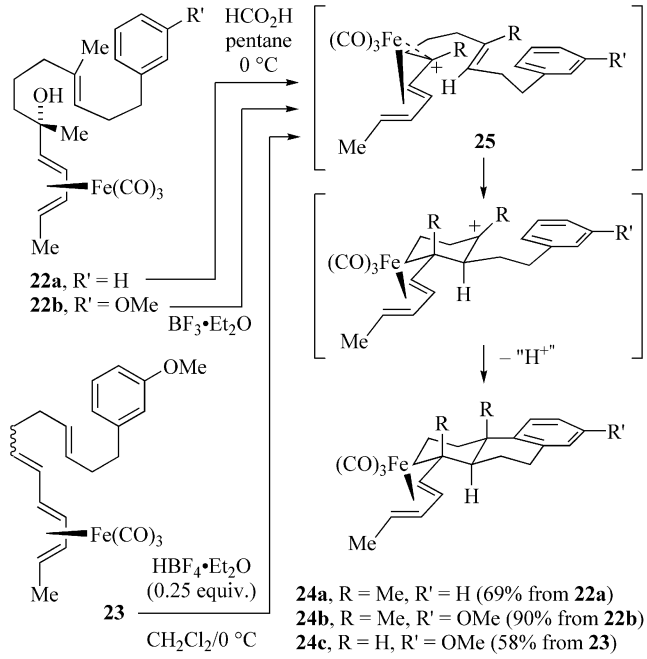
Acyclic (pentadienyl)iron(1+) cations **2** are most commonly prepared by ionization of (pentadienol)- or (pentadienyl ether)iron complexes under protic or Lewis acid conditions (Scheme 4).[2,4] Ionization of the hydroxy group occurs with anchimeric assistance from iron to generate the *transoid* pentadienyl cation **21**; subsequent isomerization of **21** occurs with retention of configuration about the C1–C2 bond.[14] In certain cases, the *transoid* pentadienyl iron cation generated in situ can undergo attack by weak nucleophiles present in the reaction mixture. These reactions generally proceed through attack at C1 on the face opposite to iron.



Scheme 4. Preparation of acyclic (pentadienyl)iron cations.

transoid (Pentadienyl)iron Cations Generated in Situ as Initiators for Polyene Cyclization

Both the Pearson[15] and the Franck-Neumann[16] groups have reported polyene cyclizations initiated by *transoid* (pentadienyl)iron cations generated in situ (Scheme 5). These cyclizations may be terminated by attack by fluoride ion, formate ion, or pendant electron-rich aromatic groups. The reactions of, for example, dienol complexes **22a** or **22b**[16b] or the conjugated triene **23**[15c] under either protic or Lewis acidic conditions resulted in the diastereoselective formation of the octahydrophenanthrene skeletons **24a**–**c**. The relative configurations of **24a** and **24b** were determined by X-ray crystallography, whereas the relative configuration of **24c** was assigned on the basis of extensive NMR spectral analysis of the free ligand (prepared by oxidation of **24c** with excess Me_3NO). The cyclizations were found to occur

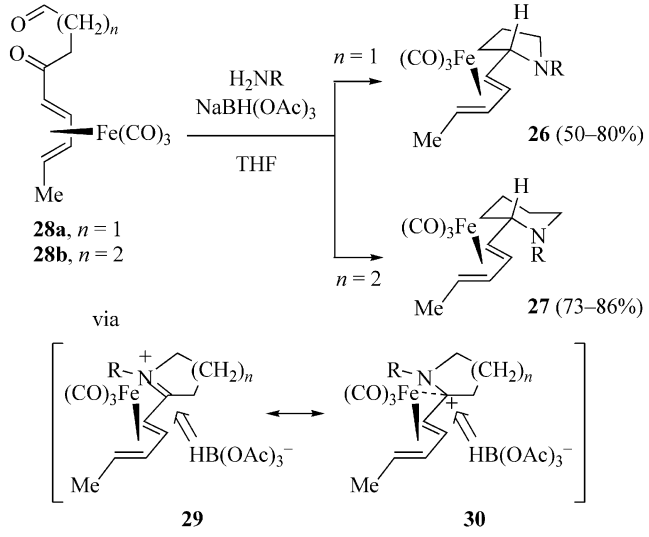


Scheme 5. Polyene cyclizations initiated by a *trans*-(pentadienyl)-iron cation.

in a diastereoselective fashion; initial C–C bond formation occurred on the *transoid* (pentadienyl)iron cation (**25**) on the face opposite to the sterically bulky $Fe(CO)_3$ group.

Diastereoselective Preparation of Dienylpyrrolidines and Dienylpiperidines

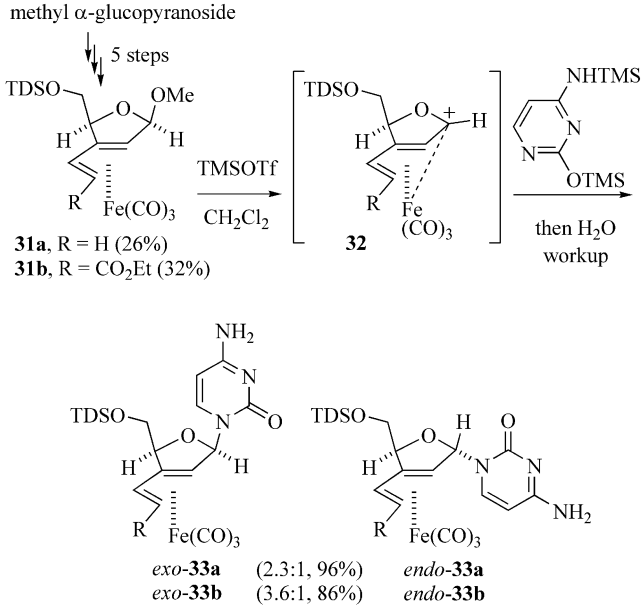
Cox and co-workers have reported on the diastereoselective preparation of dienylpyrrolidine and dienylpiperidine complexes (**26** and **27**, respectively, Scheme 6) by the reductive amination of keto aldehydes **28a** and **28b**.[17] It is proposed that these reactions proceed through reductive amination at the aldehyde, followed by generation of the iminium complexes **29** (alternative resonance contributors would be the *transoid* pentadienyl iron cations **30**). The iminium ion/pentadienyl cation complexes are each preferentially oriented as the *s-trans* conformer about the diene-to-iminium carbon so as to minimize repulsion between the diene and the substituent R on nitrogen. The approach of hydride towards the face opposite to iron (followed by rotation about the diene to pyrrolidine/piperidine bond) generated the products with excellent diastereoselective control (ψ-*exo* diastereomer).[18] The relative configurations of **26** and **27** were confirmed by X-ray crystal structures of one example of each.



Scheme 6. Reductive amination of diene keto aldehyde complexes.

Preparation of Organoiron Nucleoside Analogues

Schmalz and co-workers reported on the preparation of organoiron-containing nucleoside analogues by treatment of the dienylether complexes **31a** or **31b** (prepared in five steps from α-methyl glucopyranoside) with silylated nucleobases in the presence of trimethylsilyl triflate (Scheme 7).[19] This reaction presumably proceeds through the intermediacy of the *transoid* pentadienyl cations **32**. Nucleophilic attack on **32** occurs predominantly on the face opposite to the sterically bulky $Fe(CO)_3$ group to afford *exo*-**33a** or *exo*-**33b** as the major products, along with lesser amounts of the diastereomeric *endo* complexes. Complexes *exo*-**33a** and *exo*-**33b** were found to be cytotoxic against cultivated BJAB tumor cells (IC_{90} = 30 and 20 μM, respectively). The cytotoxicity of *exo*-**33b** was attributed to its ability to induce apoptosis by DNA fragmentation. Notably, the free ligand of complex *exo*-**33b** exhibited considerably diminished cytotoxicity (IC_{90} > 100 μM), indicating a critical, but as yet undetermined, role for the metal.

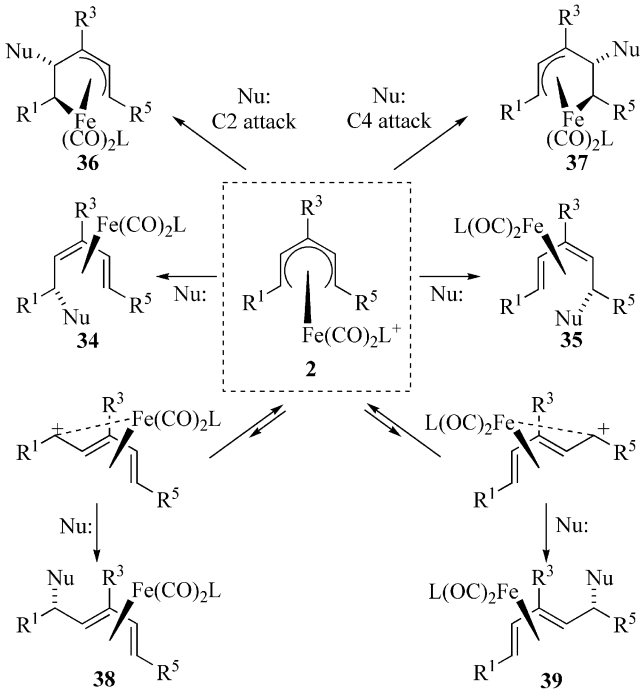


Scheme 7. Preparation of organoiron nucleoside analogues (TDS = thexyldimethylsilyl).

Reactivity of Isolable *cisoid* (Pentadienyl)iron Cations

The acyclic (pentadienyl)iron(1+) cations **2** can act as excellent organometallic electrophiles toward a wide variety of nucleophiles. Nucleophilic attack can take place on the *cisoid* form of the pentadienyl cation at either terminus, to afford the *E*,*Z*-diene complexes **34** or **35**, or on the internal atoms of the ligand (C2/C4) to afford complexes **36** or **37** (Scheme 8). Alternatively, because the *transoid* form exists in equilibrium with the *cisoid* form, nucleophilic attack on the *transoid* pentadienyl cation generates *E*,*E*-diene complexes **38** or **39** as single diastereomers. The regioselectivity for nucleophilic attack depends on the natures of the substituents present on the pentadienyl ligand, as well as on the "spectator" ligand L, the nature of the nucleophile, and even the nucleophile counterion. Although not all of these factors are well understood, a few generalities can be made.[20] *In general for tricarbonyl-ligated cations* **2** *(L = CO)* and weak neutral nucleophiles (e.g., H_2O, alcohols, arylamines, electron-rich aromatics, allylsilanes), the reactions proceed via the higher-energy (and thus more reactive) *transoid* pentadienyl forms to afford products **38**/**39**. The reactions of more reactive organocadmium reagents, organ-

ocuprates, phosphanes, or alkylamines proceed through attack at the terminal carbons of the *cisoid* conformer to give products **34**/**35**. These reactions are believed to be under frontier orbital control. If the pentadienyl ligand bears a terminal electron-withdrawing group (e.g., $R^1 = CO_2Me$), reactions with methyllithium, alkenyl Grignards, potassium phthalimide, or stabilized carbon nucleophiles proceed by attack at C2/C4, and this regioselectivity is believed to be due to charge control (i.e., nucleophilic attack at the pentadienyl carbon bearing the greatest partial positive charge). For cations in which the substituents are neither strongly electron-withdrawing nor electron-donating, nucleophilic attack frequently does not occur in a regioselective fashion. There are considerably fewer cases of acyclic (pentadienyl)iron cations bearing a phosphane ligand (i.e. **2**, L = PR_3), but in these cases the regioselectivity is generally improved over that of their corresponding $Fe(CO)_3$ cations, due to the greater stabilities/decreased reactivities of the $Fe(CO)_2PR_3$ cations.



Scheme 8. Modes of reactivity for isolable (pentadienyl)iron cations.

Synthetic Studies on Diterpenes Containing (3*Z*)-3-Methylpenta-1,3-dienyl Side-Chains

Heteroscyphic acids A and B are novel clerodane-type diterpenes isolated from cultured cells of the liverwort *Heteroscyphus planus*, structural assignments of which (**40a**/**40b**, Figure 3) were based on their MS and NMR spectroscopic data.[21a–21c] In particular, the 12*Z* stereochemistry was assigned to **40b** on the basis of NOEs between Me-16 and H-12 and between H-14 and H11. Although no biological activity was reported for **40a** or **40b**, these compounds are nonetheless structurally related to the clerodane caseargrewiin D[21d] (**42**), which exhibits both antimalarial and antitumor activity.

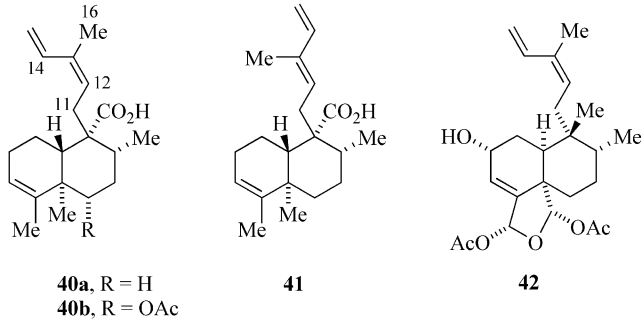
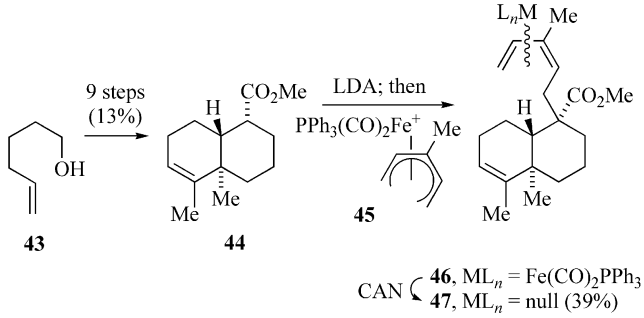


Figure 3. Proposed (**40a**) and revised (**41**) structures for heteroscyphic acid A, and structure of caeswaregiin D (**42**).

Donaldson's group envisioned introduction of the (3*Z*)-3-methyl-1,3-dienyl side-chain by nucleophilic addition to a (3-methylpentadienyl)iron cation.[22] To this end, hex-5-en-1-ol (**43**) was transformed into the decahydronaphthalene ester **44** (Scheme 9), the fused bicyclic skeleton being formed by a Mn-mediated oxidative radical cyclization.[23] Generation of the ester enolate anion from **44** and addition to the $Fe(CO)_2PPh_3$-ligated pentadienyl cation **45** gave complex **46**. This was produced as a mixture of diastereomers, due to nucleophilic attack at one or the other pentadienyl terminal carbons of the symmetrical cation. Decomplexation of **46**, followed by purification by $AgNO_3$-impregnated silica gel, gave **47** as a single diastereomer. It was surprising to note that the NMR spectroscopic data for the dienyl side chain of **47** [confirmed as *Z* by comparison of its NMR spectroscopic data with those for other known diterpenes possessing (3*Z*)-3-methyl-1,3-dienyl groups] did not match well with those reported for the heteroscyphic acids A and B. In fact, the chemical shifts reported for heteroscyphic acids A and B are more consistent with those observed for a number of diterpenes possessing (3*E*)-3-methyl-1,3-dienyl groups, and so it was suggested that the heteroscyphic acids have this geometry for the side chain (cf. **41**, Figure 3). This methodology might prove useful for the introduction of the (3*Z*)-3-methyl-1,3-dienyl side chain in **42**.



Scheme 9. Synthesis of a (3*Z*)-3-methylpenta-1,3-dienyl diterpene skeleton.

Synthetic Studies on Macrolactin A

Macrolactin A (**48**, Figure 4) is a polyene macrolide aglycon originally isolated from a taxonomically unidentified marine bacterium.[24] More recently, other members of this family of 24-membered macrolides have been isolated from *Bacillus* sp. Sc026, *Bacillus* sp. PP19-H3, and *Actinomadura* sp.[25] Initial screening revealed that **48** displays antibacterial, antiviral, and antitumor activity. The complex structure of macrolactin A presents several synthetic challenges, including four sp^3 asymmetric centers and three conjugated dienes. Several groups have reported synthetic studies,[26] including total syntheses by the groups of Smith,[27b] Carreira,[27c] and Marino.[27d]

Takemoto's group prepared the C1–C15 segment of macrolactin A, in racemic form, by utilizing the $Fe(CO)_3$ group as a mobile chiral auxiliary.[28] The synthesis begins with the achiral (hexa-2,4-dienedial)$Fe(CO)_3$ complex **49** (Scheme 10). Condensation of **49** with the enolate anion derived from ethyl acetate proceeded in a diastereoselective fashion to afford a separable mixture of the predominating ψ-*exo* β-hydroxy ester *rac*-**50** along with the ψ-*endo* alcohol *rac*-**51**. Treatment of the derived TBS ether **52** with diethyl phosphorocyanidate gave the crude cyanophosphate **53** as a mixture of diastereomers, which were used in the next step without further purification. Protonation of **53** with HBF_4 in the presence of 4-fluorobenzenethiol afforded the *E*,*Z*-dienylnitrile complex **55**, along with a minor amount of the corresponding *E*,*E*-diene complex. This 1,2-migration of iron presumably proceeds through the intermediacy of the *cisoid* (pentadienyl)iron cation **54**. The success of this reaction was highly dependent on the solvent and acid used; use of BF_3–diethyl ether gave greatly diminished yields of **55** at the expense of the formation of a variety of other nucleophilic addition products. Similarly, attempts to use hydride nucleophiles (Et_3SiH or $NaBH_3CN$) in the formation of **54** in situ were unsuccessful. Treatment of **55** with six equivalents of DIBAL, followed by quenching with aqueous NH_4Cl, resulted in reduction of the nitrile and the ester to an aldehyde and a primary alcohol, respectively. After protection of the primary alcohol as an acetate, addition of the organozinc reagent prepared from propargyl bromide and zinc in the presence of NH_4Cl gave an equimolar mixture of the diastereomeric dienol complexes ψ-*exo* **56** and ψ-*endo* **57**. Separation of the diastereomers was possible after protection as their TBS ethers **58** and **59**. Rh-catalyzed hydroboration of ψ-*exo*-**58** with pinacolborane gave the crude *E*-vinylboronate **60** in modest yield. Pd-catalyzed coupling of **60** with ethyl (*Z*)-3-iodopropenoate afforded a

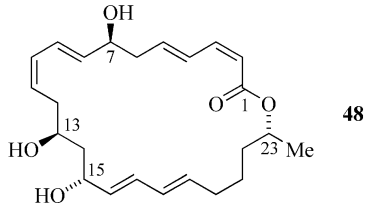
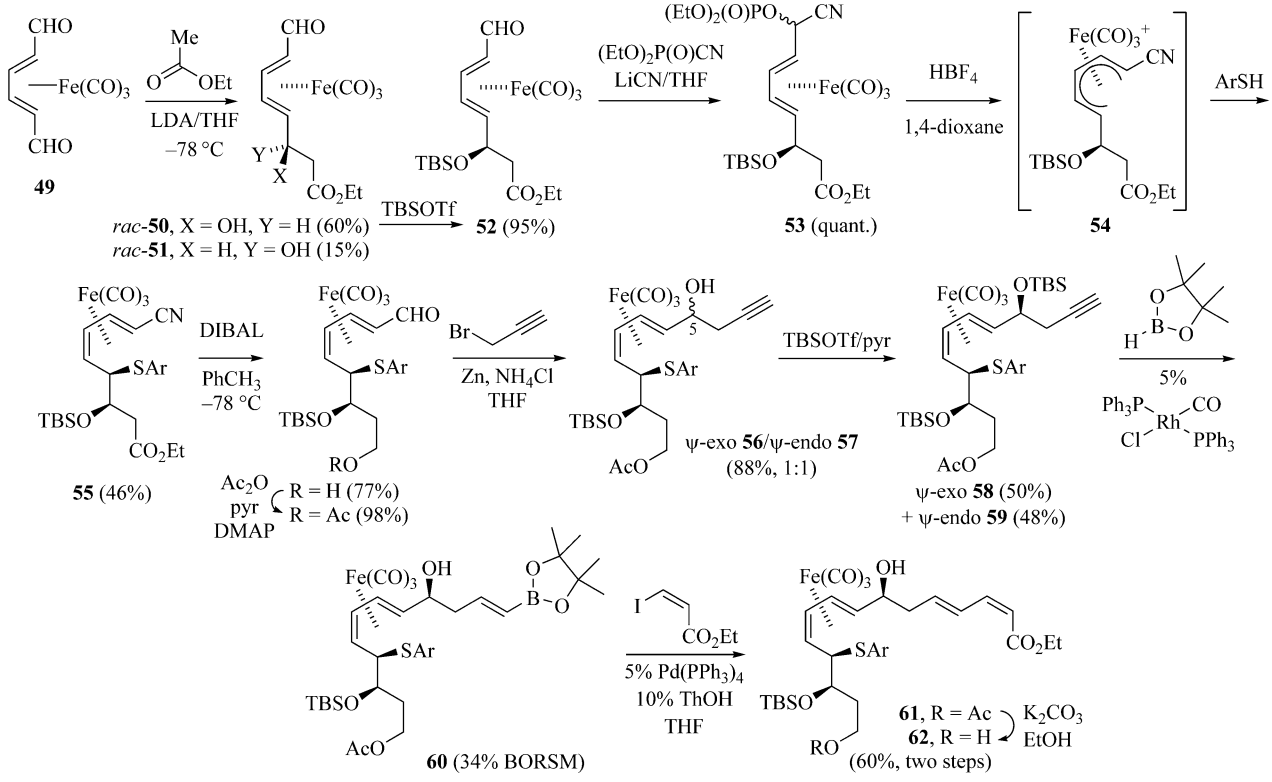


Figure 4. Structure of macrolactin A (**48**).



Scheme 10. Takemoto's synthesis of the C1–C15 segment of macrolactin A (Ar = *p*-FC_6H_4).

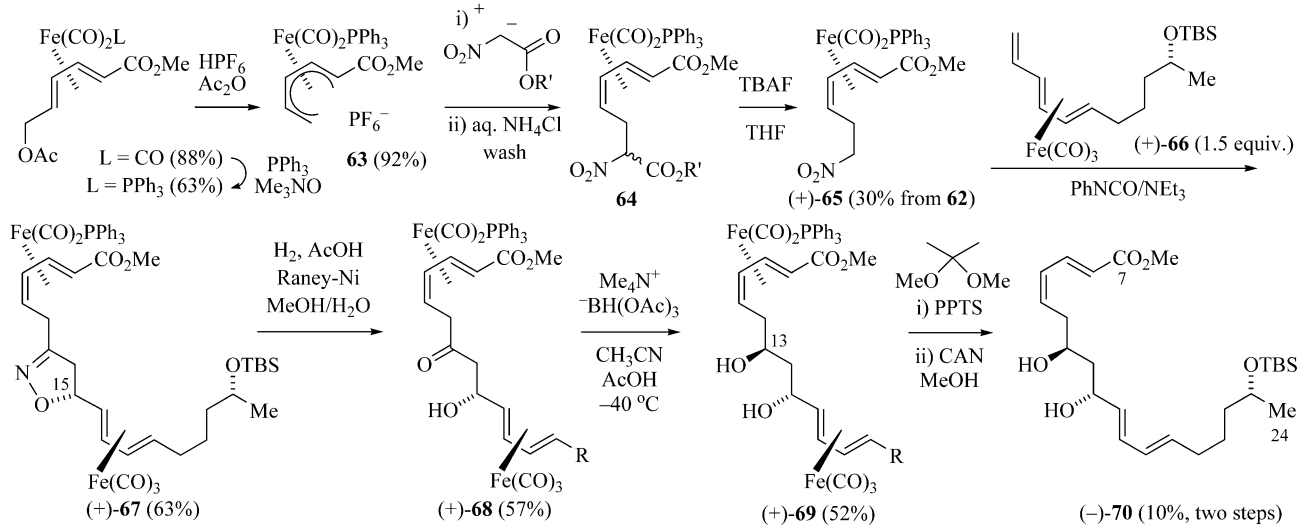
mixture of acetate **61** and alcohol **62**. Hydrolysis of **61** afforded the (2*Z*,4*E*,8*E*,10*Z*)-pentadecatetraenyl complex **62** in 60% overall yield from **60**. Unfortunately, although the primary alcohol of **62** could be oxidized with IBX, attempts to couple the resultant aldehyde with an alkenylzirconium reagent, to generate the C15–C16 bond, were unsuccessful.

Li and Donaldson have also applied diene-iron complexes to the synthesis of the C7–C24 segment of macrolactin A in enantiomerically enriched form (≥ 90% *ee*) (Scheme 11).[29] The generation of the 8*E*,10*Z*-diene segment of macrolactin utilized nucleophilic addition to the enantiomerically enriched $Fe(CO)_2PPh_3$-ligated cation **63**. This cation was prepared by standard procedures from an enantiomerically pure methyl 6-oxohexa-2,4-dienoate complex.[30] Addition of nitroacetate anion proceeded at an internal pentadienyl carbon under kinetic control, but a brief workup of the initially formed (pentenediyl)iron complex with aqueous NH_4Cl gave the *E*,*Z*-dienoate complex **64** as a mixture of diastereomers. This isomerization is believed to proceed by protonation at the ester carbonyl, dissociation to the (pentadienyl)$Fe(CO)_2PPh_3^+$ cation, and subsequent attack at the terminal position to generate the more thermodynamically *E*,*Z*-dienoate complex. Cleavage of the trimethylsilylethoxy ester from **64** and subsequent decarboxylation generated the C7–C13 segment (+)-**65**. Generation of the nitrile oxide from (+)-**65** under Mukiayama conditions[31] in the presence of 1.5 equivalents of the enantiomerically enriched triene complex (+)-**66**[32] (≥ 90% *ee*) gave the bimetallic tetraene isoxazoline (+)-**67** as a single diastereomer. The selective formation of the ψ-*exo* diastereomer in this intermolecular cycloaddition is due to the approach of the nitrile oxide at the less hindered face of the *s*-*trans* triene rotomer.[33]

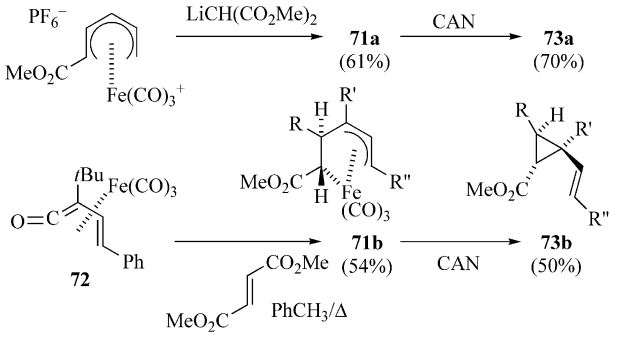
Reductive hydrolysis of isoxazoline **67**, with use of commercially purchased Raney nickel, gave the bimetallic β-hydroxy ketone (+)-**68**. With this less reactive form of the catalyst, the two iron adjuncts serve to protect the diene segments against hydrogenation.[34] Diastereoselective reduction[35] of **68** gave the diol (+)-**69**, and generation of the acetonide followed by oxidative decomplexation with CAN gave the tetraene (–)-**70**. Oxidative removal of the two iron moieties was accompanied by cleavage of the acetonide group by the acid generated under these reaction conditions. The diminished yield for this last step may be due to the lability of this tetraenyldiol; others have also reported that removal of hydroxy protecting groups from intact macrolactin A has proven difficult.[27b] In this synthesis of the C7–C24 segment, the iron-carbonyl adjuncts are responsible for *i*) stereoselective preparation for the C8–C11 *E*,*Z*-diene, *ii*) diastereoselective generation of the C23 alcohol by remote asymmetric induction, *iii*) introduction of the C15 stereocenter by a highly diastereoselective intermolecular nitrile oxide-olefin cycloaddition, and *iv*) protection of the C8–C11 and C16–C19 dienes during reductive hydrolysis of the isoxazoline group.

Synthesis of Vinylcyclopropanes

(Pent-3-ene-1,5-diyl)iron complexes **71a**, each bearing an electron-withdrawing group at C1, have been prepared by addition of carbon nucleophiles to (pentadienyl)iron(1+) cations (Scheme 12).[36] Alternatively, the thermal reaction between the (vinylketene)iron complex **72** and dimethyl fumarate generated the (pentenediyl)iron complex **71b**.[37] Oxidation of either **71a** or **71b** with ceric ammonium nitrate gave the vinylcyclopropanecarboxylates **73a** or **73b**.[36a,37] These are formally oxidatively induced reductive eliminations, so the reactions generally proceed with retention of configuration at the two centers undergoing C–C bond formation.



Scheme 11. Synthesis of the enantiomerically enriched C7–C24 segment of macrolactin A [R = $CH_2CH_2CH_2CH(OTBS)Me$, R′ = CH_2CH_2TMS].



Scheme 12. Synthesis of vinylcyclopropanes by oxidative decomplexation of (pent-3-ene-1,5-diyl)iron complexes [**a**, R = $CH(CO_2Me)_2$, R′ = R′′ = H; **b**, R = CO_2Me, R′ = *t*Bu, R′′ = Ph].

Synthesis of 2-(2-Carboxycyclopropyl)glycines and Dysibetaine CPa

The selective activation of different glutamate receptors may depend on recognition of particular conformers of this flexible molecule. For this reason, the synthesis and evaluation of a number of 2-(2′-carboxycyclopropyl)glycines (e.g., **74a**–**f**, Figure 5) as conformationally restricted analogues of glutamate has led to the discovery of ligands with mGluR specificity.[38] In particular, the extended conformation, as exemplified by compounds **74a**–**d**, is believed to be a requirement for binding to the mGluR1 and mGluR2 receptors. Recently, Sakai and co-workers isolated a novel water-soluble cyclopropane-containing betaine from *D. herbacea*, which they termed dysibetaine CPa (**75**, Figure 5).[39] Compound **75** displaced kinate from the NMDA-type glutamate receptor with IC_{50} = 13 μM.

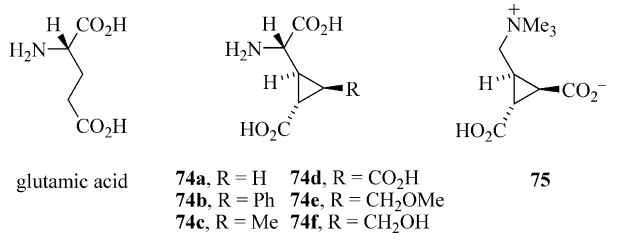
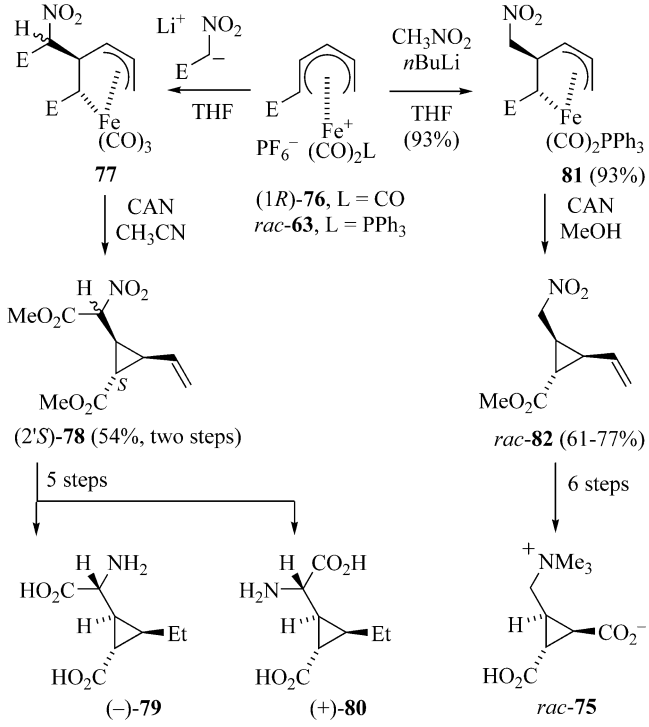


Figure 5. Structures of conformationally restricted glutamate analogues (**74**) and dysibetaine CPa (**75**).

Treatment of the enantiomerically enriched tricarbonyl-ligated cation (1*R*)-**76** (≥80% *ee*) with the anion generated from methyl nitroacetate gave the (pentenediyl)iron complex **77** as a mixture of diastereomers at the nitroacetate carbon (Scheme 13).[36a] Decomplexation of the mixture of diastereomers afforded vinylcyclopropanecarboxylate (2′*S*)-**78** as an inseparable mixture of diastereomers at the nitroacetate carbon. Transformation of the diastereomeric mixture (2′*S*)-**78** into the individual 3-ethyl CCGs (–)-**79** and (+)-**80** required reduction of the vinyl and nitro groups, conversion of the amines into a separable mixture of diphenylmethylene imines,[40] hydrolysis of the separate diphenylmethylene imines and the methyl esters, and finally generation of the free bases.

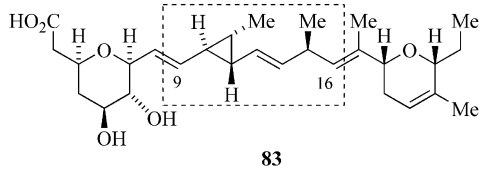


Scheme 13. Synthesis of 2-(2′-carboxycyclopropyl)glycines and dysibetaine CPa (E = CO_2Me).

For the preparation of dysibetaine CPa, treatment of the dicarbonyl(triphenylphosphane)-ligated cation *rac*-**63** with the anion generated from nitromethane gave the (pentenediyl)iron complex **81** in excellent yield (Scheme 13).[41] Oxidative decomplexation of **81** gave the vinylcyclopropanecarboxylate **82**. Transformation of **82** into *rac*-**75** required conversion of the vinyl functionality into an ester, subsequent reduction of the primary nitro group, hydrolysis, and exhaustive methylation.

Synthesis of the C9–C16 Segment of Ambruticin

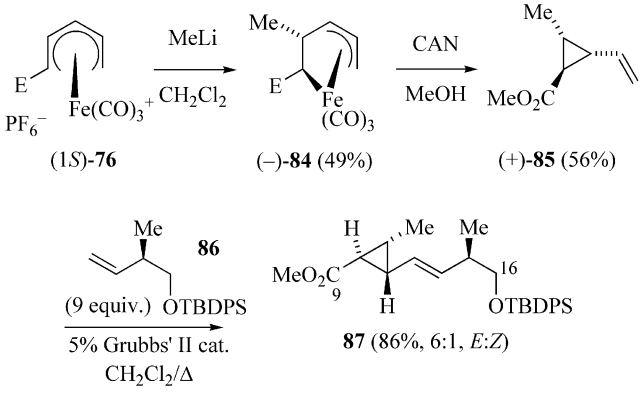
Ambruticin (**83**, Figure 6), a structurally unique carboxylic acid isolated from *Polyangium cellulosum var fulvum*, exhibits potent oral antifungal activity against *Coccidioides immitis*, *Histoplasma capsulatum*, and *Blastomyces dermititidis*.[42] The complex structure of ambruticin, including a tetrahydropyranyl ring, a dihydropyranyl ring, and a divinylcyclopropane ring, presents several synthetic challenges. Several groups have reported synthetic studies,[43] including total syntheses by the groups of Kende,[44a] Jacobsen,[44b] Martin,[44c] and Lee.[44d]



83

Figure 6. Structure of the antifungal agent ambruticin (**83**).

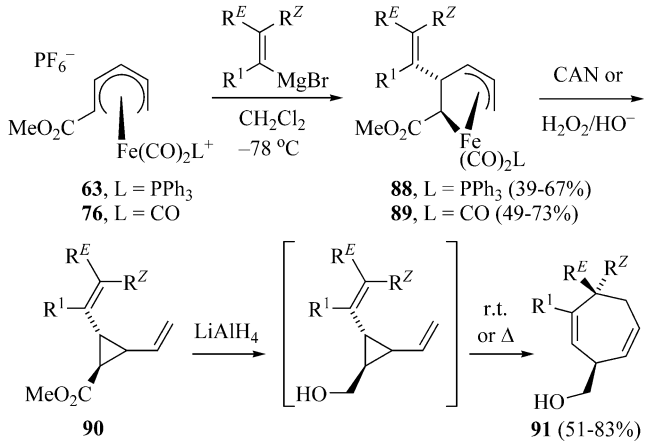
Treatment of (1*S*)-**76** in CH_2Cl_2 with a ethereal solution of methyllithium gave the (pentenediyl)iron complex (–)-**84** along with minor amounts of tricarbonyl(methyl-3,5-hexadienoate)iron (Scheme 14).[45] It was found that use of CH_2Cl_2 as solvent was crucial to the success of this reaction. Use either of ether or of THF gave reduced yields of the (pentenediyl)iron complex. Oxidative decomplexation of (–)-**84** cleanly gave the stereodefined vinylcyclopropanecarboxylate (+)-**85**. Cross metathesis of **85** with a ninefold excess of (*R*)-**86** in the presence of the second-generation Grubbs catalyst (5 mol-%) gave **87** as a mixture of *E* and *Z* isomers (6:1 ratio).[46]



Scheme 14. Synthesis of the C9–C16 segment of ambruticin (E = CO_2Me).

Synthesis of Divinylcyclopropanes and Cope Rearrangement

Donaldson and co-workers demonstrated that the reactions between (2-methoxycarbonylpentadienyl)iron(1+) cations **63** or **76** and alkenyl Grignard reagents primarily gave the corresponding (2-alkenylpent-3-ene-1,5-diyl)iron complexes **88** or **89**, respectively (Scheme 15).[47] The yields of these products were dependent on the reaction media; use of dichloromethane gave the best results, whereas use of THF or toluene led to diminished yields of **88/89**. Nucleophilic attack on the face opposite to the metal was corroborated by the X-ray crystal structure of the parent complex **89** ($R^1 = R^E = R^Z = H$).[47b] Oxidative decomplexation of **88/89** gave the divinylcyclopropane **90**. In most cases CAN gave good yields of the 2,3-divinylcyclopropanecarboxylates, although for complexes with electron-rich 2-alkenyl groups secondary oxidation of the resultant divinylcyclopropane products led to diminished yields. In these cases, oxidation with alkaline hydrogen peroxide provided superior yields, but led to mixtures of both *cis*- and *trans*-divinylcyclopropanes. Reduction of **90**, followed by [3,3]-sigmatropic rearrangement,[48] afforded the (2,6-cycloheptadienyl)methanols **91**. Although the temperature required for the Cope rearrangement varied depending on the alkenyl substituents and olefin geometries, good overall yields were obtained from complexes **88/89**.



Scheme 15. Synthesis of divinylcyclopropanes and Cope rearrangement.

Synthesis of a Guianolide Skeleton

The guianolides are a family of sesquiterpenes characterized by a common 5,7,5-fused tricyclic skeleton. The majority of these compounds possess *trans*-γ-butyrolactone rings, but differ with respect to the oxygenation and oxidation state(s) of carbons 2–5, 8, 10, and 11.[49] Representative members of this family include chinesiolide B (**92**, Figure 7),[49d] cynaropikrin (**93**),[49e] and cladantholide (**94**).[49f]

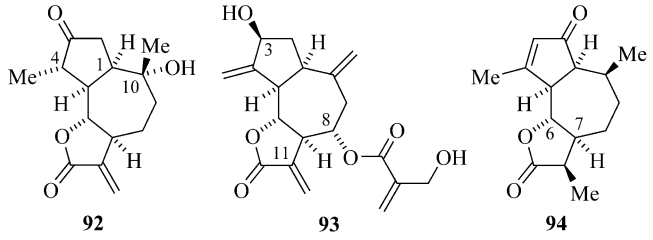
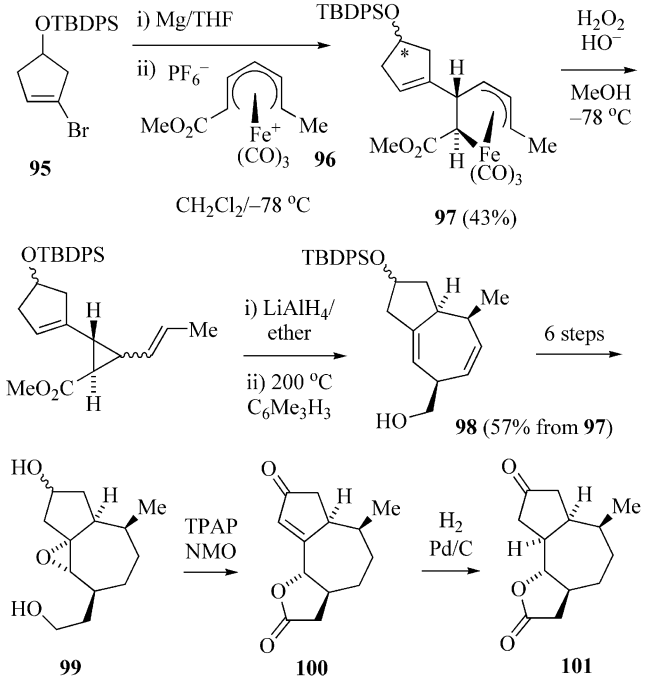


Figure 7. Representative guianolide natural products.

Donaldson and co-workers have applied organoiron methodology to the synthesis of the guaianolide 5,7,5-ring system (Scheme 16).[50] Treatment of the Grignard reagent derived from the known[51] cyclopentenyl bromide **95** with the (dienyl)$Fe(CO)_3^+$ cation **96**[52] gave the (pentenediyl)iron complex **97** as a mixture of diastereomers at the silyl ether carbon (*). Oxidative decomplexation, ester reduction, and Cope rearrangement at elevated temperatures gave **98**. The hexahydroazulene **98** was transformed into the epoxydiol **99** by *i*) selective hydrogenation of the less substituted olefin, *ii*) extension of the C3 side chain by tosylation and cyanide displacement, *iii*) cleavage of the silyl ether, *iv*) epoxidation,

and finally, *v*) twofold reduction of the nitrile side chain. Oxidation of **99** with catalytic TPAP and NMO (3.2 equiv.) gave a single lactone **100**. This transformation presumably proceeds through oxidation of both the primary and the secondary alcohols, followed by β-elimination of the epoxide, generation of a lactol, and further oxidation to the lactone. Reduction of **100** afforded **101**, which possesses the relative stereochemistry of cladantholide about the seven-membered ring.

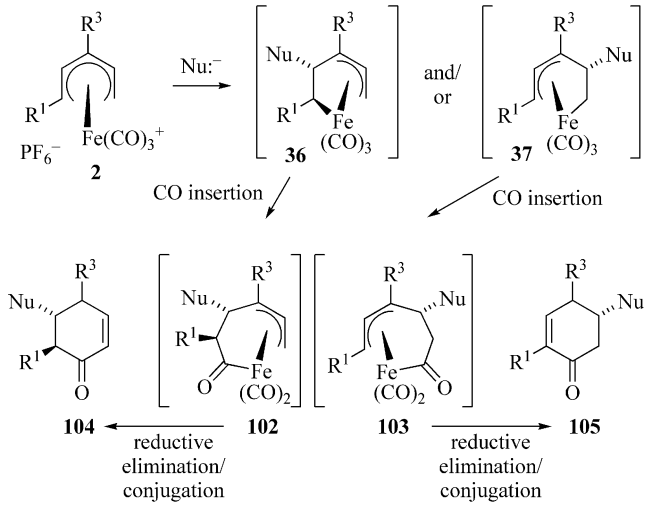


Scheme 16. Preparation of the 5,7,5 ring system of the guianolides.

Synthesis of Cyclohexenones

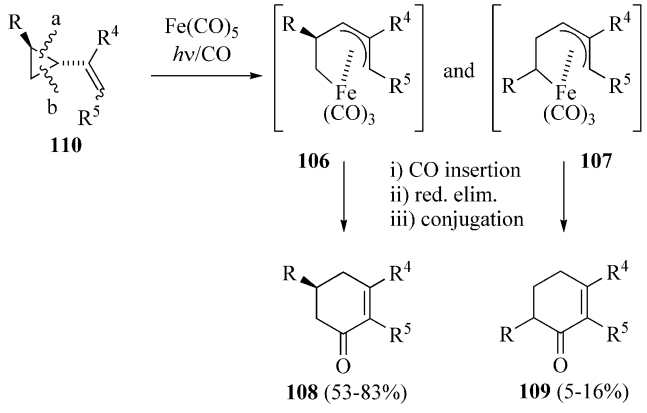
The (pentenediyl)iron complexes shown in Schemes 12–16 are stable, isolable species. This is believed to be due to the fact that the presence of an electron-withdrawing group attached to a carbon–metal σ bond slows the rate of carbonyl insertion.[53] In contrast, (pentenediyl)-iron complexes lacking an electron-withdrawing group at C1 (e.g., **36** or **37**, Scheme 17) may be generated by nucleophilic attack on acyclic (pentadienyl)iron cations at the internal C2 position.[54] These complexes are generally unstable and undergo CO insertion to generate the (acyl)iron complexes **102/103**. Reductive elimination of **102/103**, followed by conjugation of the olefin, gives cyclohexenones **104/105**, respectively.

An alternative route to cyclohexenones is through the photochemically initiated ring rearrangement–carbonylation of alkenylcyclopropanes (Scheme 18).[55] Although this reaction does not formally involve a (diene)iron complex or (dienyl)iron cation, it is nonetheless related by the presumed intermediates. This reaction is believed to proceed through oxidative insertion of iron into one of the proximal vinylcyclopropane bonds (b or a) to generate

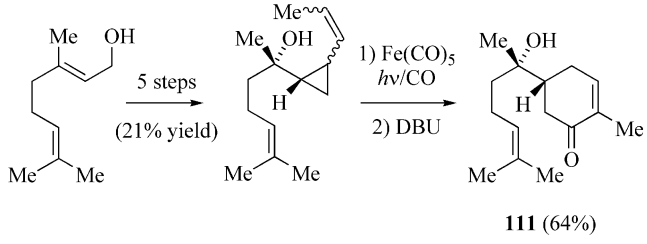


Scheme 17. Generation of cyclohexenones from (pentadienyl)iron cations.

(pentenediyl)iron intermediates **106** or **107**, respectively. Carbonyl insertion, followed by reductive elimination and conjugation, gives **108** or **109**. Isolation of **108** as the major cyclohexenone product indicates that insertion into the cyclopropane bond "b" is favored. Because the major product arises from cleavage of the less substituted vinylcyclopropane bond "b", use of the enantiomerically enriched (>99% *ee*) vinylcyclopropane **110** (R = CH_2OBn, R^4 = R^5 = H) as starting material led to **108** in enantiomerically en-



Scheme 18. Generation of cyclohexenones through iron-mediated carbonylation of alkenylcyclopropanes.



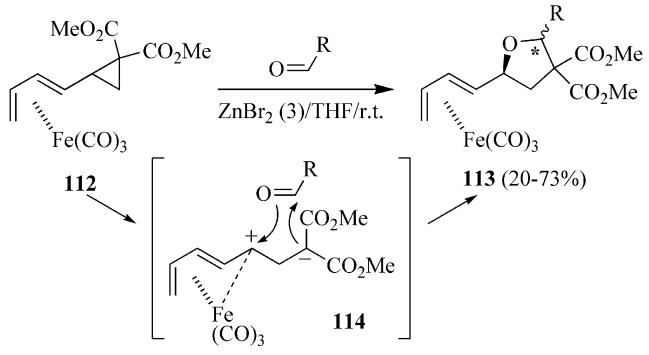
Scheme 19. Taber and co-workers' synthesis of (–)-delobanone.

riched form (>95% *ee*). The enantiomeric excess and absolute configuration of the minor product **109** was not identified.

Taber and co-workers have applied this methodology to the enantioselective synthesis of (–)-delobanone (**111**), beginning with geraniol (Scheme 19).[55d]

Miscellaneous

Christie and co-workers have reported 1,3-dipolar cycloadditions between aldehydes and the racemic dienylcyclopropane complex **112** in the presence of $ZnBr_2$ (Scheme 20).[56] This reaction affords the dienylfurans **113** as mixtures of two (of the four possible) diastereomers. In all cases, the relative configurations at the iron-diene and the tetrahydrofuranyl carbon adjacent to the diene were found to be as indicated (i.e., ψ-*exo*), so the products formed are due to the *cis*- and *trans*-2,4-disubstituted furan ring at the indicated carbon (*). The authors propose that this reaction proceeds through the formation of the zwitterionic intermediate **114**, which reacts with the aldehyde on the face opposite to the sterically bulky (tricarbonyl)iron adjunct.



Scheme 20. Formation of polysubstituted dienyltetrahydrofurans.

Conclusions

Complexation of diene and dienyl ligands to iron facilitates the stereoselective preparation of conjugated *E*,*E*- and *E*,*Z*-1,3-dienes, trisubstituted cyclopropanes, 1,4-cycloheptadienes, and cyclohexenones. These features of the (tricarbonyl)iron adjuncts have been exploited by a number of research groups for the synthesis of polyene macrolides, optical pigment chromophores, heterocycles, terpenes, conformationally restricted ligands for glutamate receptors, and antifungal agents.

Acknowledgments

W. A. D. is grateful to his co-workers whose research accomplishments are described in this review. Their experimental skill, dedication, and keen observation turned ideas into reality. Financial support over the years from the National Institutes of Health (GM-42641) and the National Science Foundation (NSF) (CHE-0415771) is gratefully acknowledged.

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