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

William A. Donaldson[a] and **Subhabrata Chaudhury**[a]

William A. Donaldson: william.donaldson@marquette.edu

[a] Department of Chemistry, Marquette University, P. O. Box 1881, Milwaukee, WI 53201-1881 USA, Fax: 414-288-7066

Abstract

Complexation of (tricarbonyl)iron to an acyclic diene serves to protect the ligand against oxidation, reduction and cycloaddition reactions while the steric bulk of this adjunct serves to direct the approach 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. pentadienyl-iron cations). Recent applications of these reactivities to the synthesis of polyene, cyclopropane, cycloheptadiene and cyclohexenone containing natural products or analogs will be presented.

Keywords

Diene ligands; Iron; Synthetic methods; Regioselective nucleophilic addition

Introduction

While 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 towards catalytic reduction and cycloaddition reactions.[1b] Their structural assignment was eventually corroborated by X-ray crystallography in 1963.[1c] At about this 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 have appeared concerning the use of complexes of type **3** and **4**.[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 will focus on chemistry related to complexes **1** and **2** from 2000 forward.

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** which utilized $Fe(CO)_3$ to protect a 3,5-hexadienoic acid against conjugation.[6] The synthesis begins with conversion of protected 4-penten-1,2,3-triol **6** into the tetrahydrofuranyl alcohol **7** in eight steps. Key steps in this sequence included a Johnson

Correspondence to: William A. Donaldson, william.donaldson@marquette.edu.

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orthoester Claisen rearrangement to form the C9–C10 olefin and a [3+2] annulation[7] using an allylsilane to form the *cis*-tetrahydrofuranyl ring. Attempts at esterification of **7** with 2-methyl-3,5-hexadienoic acid were unsuccessful and generally led to recovery of **7** and the *conjugated* diene, 2-methyl-2,4-hexadienoic acid. Alternatively, esterification of (2*S*,3*R*) (2-methyl-3,5-hexadienoic 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] with Grubbs' 1st generation catalyst afforded the macrolide ring **10** exclusively as the 3*E*,5*E*,9*E*-stereoisomer. Completion of the synthesis involved hydrostanallation of the alkyne, conversion to the 2-alkenyl iodide, cleavage of the protecting groups and Pd-catalyzed coupling.

During the course of this work, Va and Roush discovered that the esterification of the diastereomeric (2*S*,3*S*) (2-methyl-3,5-hexadienoic 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 via dehydration to generate the ketene intermediate **13**; addition of the alcohol generates the ketene hemiacetal **14**. Protonation of **14** occurs via the *s*-trans conformer and on the face opposite to the sterically bulky $Fe(CO)_3$ group. Notably, the *relative* configurations at C2,C3 of **9** and **12** are the same (i.e. 2*S*,3*R* compared to 2*R*,3*S*), and thus it is likely that the transformation of **8** to **9** proceeds via the enantiomeric ketene (*ent*-**13**).

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–b] The synthesis begins with a nitrile aldol reaction of (β-ionone)$Fe(CO)_3$ (**16**) with acetonitrile. This reaction proceeds with migration of the iron fragment to give **17**. 1,3-Migration of the tricarbonyliron group have previously been observed.[4g,12] The presence of a terminal electron-withdrawing substituent (e.g. –CN) and the use of excess nucleophile generally lead 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 labelled 11*Z*-retinals **15b d**; examination of the labelled retinals by solid state ^2H NMR spectroscopy provided information on the orientation of these molecules in the rhodopsin binding pocket.[11c]

The rationale for *Z*-selective Peterson olefination rests on approach of the anion of trimethylsilylacetate to **18** in 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 the steric repulsions between the bulky TMS group and the (diene)$Fe(CO)_3$ group. *Syn*-elimination from the resultant β-silylalcohol,[13] as is known for anionic conditions, results preferentially in the 11*Z*-stereoisomer.

Reactivity of *In situ* Generated Transoid (Pentadienyl)iron(1+) Cations

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 hydroxyl 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 *in situ*

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generated transoid pentadienyl iron cation can undergo attack by weak nucleophiles present in the reaction mixture. These reactions generally proceed via attack at C1 on the face opposite to iron.

In situ generated transoid (pentadienyl)iron cations as initiators for polyene cyclization

Both the groups of Pearson[15] and of Franck-Neumann[16] reported polyene cyclizations initiated by *in situ* generated transoid (pentadienyl)iron cations (Scheme 5). These cyclizations may be terminated by attack of fluoride ion, formate ion or pendant electron-rich aromatic groups. For example, reaction of dienol complexes **22a** or **b**,[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**/**b** were determined by X-ray crystallography, while 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 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 Dienyl Pyrrolidines and Piperidines

Cox and co-workers have reported on the diastereoselective preparation of dienyl pyrrolidine and dienyl piperidine complexes (**26** and **27** respectively, Scheme 6) by the reductive amination of ketoaldehydes **28a** and **28b**.[17] These reactions are proposed to proceed via reductive amination at the aldehyde, followed by generation of the iminium complex **29** (an alternative resonance contributor is the transoid pentadienyl iron cation **30**). The iminium ion/pentadienyl cation complex is preferentially oriented in the *s*-trans conformer about the diene-to-iminium carbon so as to minimize repulsion between the diene and the substituent R on nitrogen. Approach of hydride to 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 each.

Preparation of Organoiron Nucleoside Analogs

Schmalz and co-workers reported on the preparation of organoiron containing nucleoside analogs by reaction of the dienyl ether complexes **31a** or **b** (prepared in 5 steps from α-methyl glucopyranoside) with silylated nucleobases in the presence of trimethylsilyl triflate (Scheme 7).[19] This reaction presumably proceeds via intermediacy of the transoid pentadienyl cation **32**. Nucleophilic attack on **32** occurs predominantly on the face opposite to the sterically bulky $Fe(CO)_3$ group to afford *exo*-**33a** or **b** as the major product, along with a lesser amount of the diastereomeric *endo* complex. 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.

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 termini 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, since the transoid form exists in equilibrium with the cisoid form, nucleophilic attack on the transoid pentadienyl cation generates *E*,*E*-diene complexes **38** or

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39 as a single diastereomer. The regioselectivity for nucleophilic attack depends on the nature of the substituents present on the pentadienyl ligand as well as the "spectator" ligand L, the nature of the nucleophile, and even the nucleophile counter ion. While not all of these factors are well understood, a few generalities can be made.[20] *In general for tricarbonyl-ligated cations **2** (L = CO)*, weak neutral nucleophiles (e.g. H_2O, alcohols, aryl amines, electron-rich aromatics, allyl silanes) reaction proceeds via the higher energy (and thus more reactive) transoid pentadienyl forms to afford products **38**/**39**. Reaction of more reactive organocadmium reagents, organocuprates, phosphines and alkyl amines proceeds via 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. $R^1 = CO_2Me$), reaction with methyl lithium, alkenyl Grignards, potassium phthalimide and stabilized carbon nucleophiles proceeds 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 or electon-donating, nucleophilic attack frequently does not occur in a regioselective fashion. There are considerably fewer cases of acyclic (pentadienyl)iron cations bearing a phosphine ligand (i.e. **2**, L = PR_3), however in these cases the regioselectivity is generally improved over that of their corresponding $Fe(CO)_3$ cations due to the greater stability/decreased reactivity of the $Fe(CO)_2PR_3$ cations.

Synthetic Studies on Diterpenes with a 3-Methyl-1,3*Z*-pentadienyl Side-chain

Heteroscyphic acids A and B are novel clerodane-type diterpenes isolated from cultured cells of the liverwort *Heteroscyphus planus*, whose structural assignments (**40a**/**b**) were based on their MS and NMR spectral data (Figure 3).[21a–c] In particular the 12*Z*-stereochemistry for **40b** was assigned on the basis of NOEs between Me-16 and H-12 and between H-14 and H11. While no biological activity was reported for **40a** or **b**, these compounds are nonetheless structurally related to the clerodane caseargrewiin D[21d] (**41**) which exhibits both antimalarial and antitumor activity.

Donaldson's group envisioned introduction of the 3-methyl-1,3Z-dienyl side-chain by nucleophilic addition to a (3-methylpentadienyl)iron cation.[22] To this end, 5-hexen-1-ol (**43**) was transformed into the decahydronaphthalene ester **44** (Scheme 9); the fused bicyclic skeleton was 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 spectral data for the dienyl sidechain of **47** (confirmed as *Z* by comparison of its NMR spectral data to that of other known diterpenes possessing a 3-methyl-1,3*Z*-dienyl group) did not match well with that 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 a 3-methyl-1,3*E*-dienyl group, and thus it was suggested that the heteroscyphic acids have this geometry for the sidechain (c.f. **41**, Figure 3). This methodology might prove useful for the introduction of the 3-methyl-1,3*Z*-dienyl sidechain in **42**.

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.

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PP19-H3, and *Actinomadura* sp.[25] Initial screening revealed that **48** displayed 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 has prepared the C1–C15 segment of macrolactin A, in racemic form, utilizing the $Fe(CO)_3$ group as a mobile chiral auxiliary.[28] The synthesis begins with the achiral (2,4-hexadiendial)$Fe(CO)_3$ 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 predominantly the ψ-exo β-hydroxyester *rac*-**50** along with the ψ-endo alcohol *rac*-**51**. Reaction 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 via 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-etherate gave greatly diminished yields of **55** at the expense of a variety of other nucleophilic addition products. Similarly, attempts to use hydride nucleophiles (Et_3SiH or $NaBH_3CN$) in the *in situ* formation of **54** were unsuccessful. Treatment of **54** with 6 equivalents of DIBAL, followed by quenching with aqueous NH_4Cl, resulted in reduction of the nitrile and ester to an aldehyde and 1° alcohol respectively. After protection of the 1° 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**/**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 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, while the 1° alcohol of **62** could be oxidized with IBX, attempts at coupling 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).[29a] Generation of the 8*E*,10*Z*-diene segment of macrolactin utilized nucleophilic addition to the enantiomerically enriched $Fe(CO)_2PPh_3$ ligated cation **62**. This cation was prepared by standard procedures from enantiomerically pure methyl 6-oxo-2,4-hexadienoate complex.[30] Addition of nitroacetate anion **63** proceeds at an internal pentadienyl carbon under kinetic control, however a brief work-up 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 proposed to proceed via protonation at the ester carbonyl, dissociation to the (pentadienyl)$Fe(CO)_2PPh_3^+$ cation, followed by 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** using 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 approach of the nitrile oxide on the less hindered face of the s-*trans* triene rotomer.[33] Reductive hydrolysis of isoxazoline **67**, using commercially purchased Raney-nickel, gave the bimetallic β-hydroxyketone (+)-**68**. Using this less reactive form of the catalyst, the two iron adjuncts serve to protect the diene segments against hydrogenation.[34] Diastereoselective

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reduction[35] of **68** gave the diol (+)-**69**. 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 due to the acid generated under these reaction conditions. The diminished yield for this last step may be due to the lability of this tetraenyldiol as others have reported that removal of hydroxyl protecting groups from intact macrolactin A has proven to be 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

(3-Pentene-1,5-diyl)iron complexes **71a**, 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 of (vinylketene)iron complex **72** with dimethylfumarate generated the (pentenediyl)iron complex **71b**.[37] Oxidation of either **71a** or **71b** with ceric ammonium nitrate gave the vinylcyclopropanecarboxylates **73a** or **b**.[36a, 37] Since this is formally an oxidatively induced-reductive elimination, the reaction generally proceeds with retention of configuration at the two centers undergoing C–C bond formation.

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

The selective activation of different glutamate receptors may depend on recognition of a particular conformer 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 analogs 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.

Reaction of the enantiomerically enriched tricarbonyl-ligated cation (1*R*)-**76** (≥ 80% ee) with the anion generated from methyl nitroacetate gave (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.

For the preparation of dysibetaine CPa, reaction of the dicarbonyl(triphenylphosphine)-ligated cation *rac*-**62** with the anion generated from nitromethane gave (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 to an ester, subsequent reduction of the 1° nitro group, hydrolysis and exhaustive methylation.

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Synthesis of the C9–C16 Segment of Ambruticin

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

Reaction of (1*S*)-**76** in CH_2Cl_2 with a ethereal solution of methyl lithium gave the (pentenediyl)iron complex (−)-**84** along with a minor amount 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 of either ether or 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 nine fold excess of (*R*)-**86** in presence of 5 mol % of Grubbs' 2nd generation catalyst gave **87** as a mixture of *E*- and *Z*-isomers (6:1 ratio).[46]

Synthesis of Divinylcyclopropanes and Cope rearrangement

Donaldson and co-workers have demonstrated that the reaction of (2-methoxycarbonylpentadienyl)iron(1+) cations **62** or **76** with alkenyl Grignard reagents gave primarily the corresponding (2-alkenyl-3-pentene-1,5-diyl)iron complexes **88** or **89** respectively (Scheme 15).[47] The yield of these products was dependent on the reaction media; use of methylene chloride gave the best results while THF or toluene led to diminished yields of **88**/**89**. Nucleophilic attack on the face opposite to the metal was corroborated by 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-divinylcyclopropanecarboxylate, however for complexes with an electron rich 2-alkenyl group secondary oxidation of the resultant divinylcyclopropane product 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-cycloheptadienylmethanol **91**. While the temperature required for the Cope rearrangement varied depending on the alkenyl substituents and olefin geometry, good overall yields were obtained from complexes **88**/**89**.

Synthesis of a Guianolide Skeleton

The guianolides are a family of sesquiterpenes characterized by a 5,7,5-fused tricyclic skeleton. The majority of these compounds possess a *trans*-γ-butyrolactone ring, 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]

Donaldson and co-workers have applied organoiron methodology to the synthesis of the 5,7,5 ring system of the guianolides (Scheme 16).[50] Reaction of the Grignard reagent derived from known[49] cyclopentenyl bromide **95** with the (dienyl)$Fe(CO)_3^+$ cation **96**[50] 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** via *i*) selective hydrogenation of the less substituted olefin, *ii*) extension of the C3 sidechain by tosylation and cyanide displacement, *iii*) cleavage of the silyl ether, *iv*) epoxidation and finally, *v*) twofold reduction of the nitrile sidechain. Oxidation of **99** with catalytic TPAP

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and NMO (3.2 equiv) gave a single lactone **100**. This transformation presumably proceeds via oxidation of both the 1° and 2° 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 about the seven-membered ring of cladantholide.

Synthesis of Cyclohexenones

The (pentenediyl)iron complexes discussed 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 the photochemically initiated ring rearrangement carbonylation of alkenylcyclopropanes (Scheme 18).[55] While 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 proceeds via oxidative insertion of iron into one of the proximal vinylcyclopropane bonds (b or a) to generate (pentenediyl)iron intermediates **106** or **107** (respectively). Carbonyl insertion, followed 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. Since the major product arises by cleavage of the less substituted vinylcyclopropanes bond “b”, beginning with enantiomerically enriched (> 99% ee) vinylcyclopropane **110** ($R = CH_2OBn$, $R^4 = R^5 = H$) led to **108** in enantiomerically enriched 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 the 1,3-dipolar cycloaddition of aldehydes with the racemic dienylcyclopropane complex **112** in the presence of $ZnBr_2$ (Scheme 20).[56] This reaction affords the dienylfurans **113** as a mixture of two (of the four possible) diastereomers. In all cases, the relative configuration at the iron-diene and the tetrahydrofuranyl carbon adjacent to the diene were found to be as indicated (i.e. ψ-exo), and thus the formed are due to the *cis*- and *trans*-2,4-disubstituted furan ring. at the dienyl at the indicated carbon (*) in moderate yield. The authors propose that this reaction proceeds via formation of the zwitterionic intermediate **114** which reacts with the aldehyde on the face opposite to the sterically bulky (tricarbonyl)iron adjunct.

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 adjunct have been exploited by a number of research groups in the synthesis of polyene macrolides, optical pigment chromophores, heterocycles, terpenes, conformationally restricted ligands for glutamate receptors, and antifungal agents.

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Acknowledgments

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Biographies

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 was a postdoctoral fellow in the Department of Medicinal Chemistry at 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 using transition metal complexes and their application in organic synthesis.

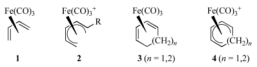

Figure 1.
Structures of diene- and dienyl-iron complexes.

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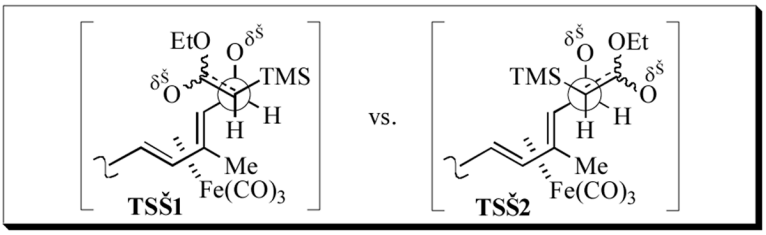

Figure 2.
Rationale for *Z*-selective Peterson olefination of **18**.

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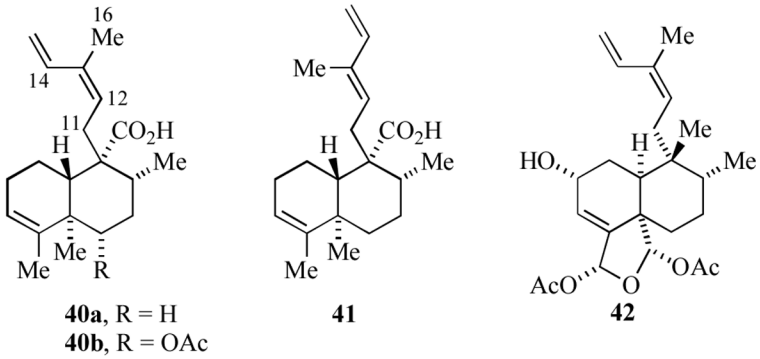

40a, R = H
40b, R = OAc

41

42

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

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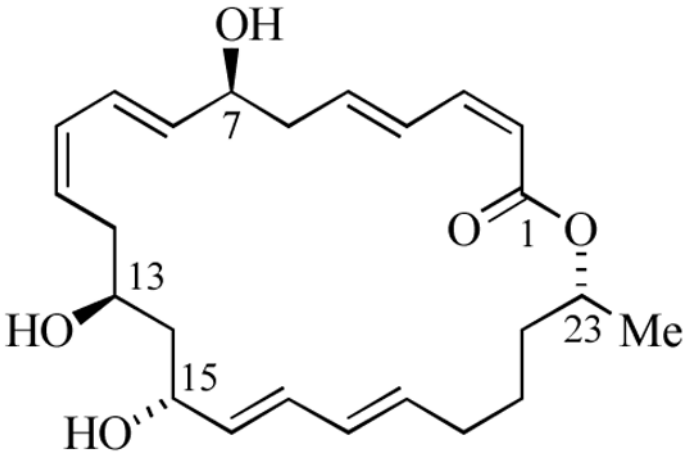

48

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

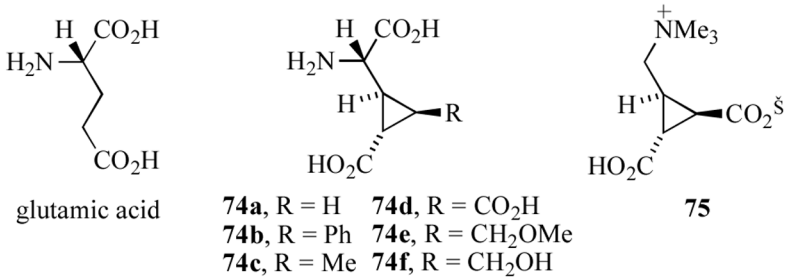

Figure 5.
Structure of conformationally restricted glutamate analogs (**74**) and dysibetaine CPa (**75**).

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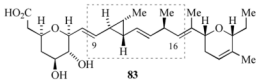

Figure 6.
Structure of the antifungal agent ambruticin (**83**).

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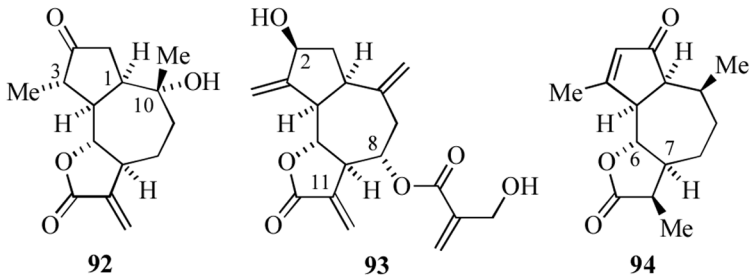

92 **93** **94**

Figure 7.
Representative guianolide natural products.

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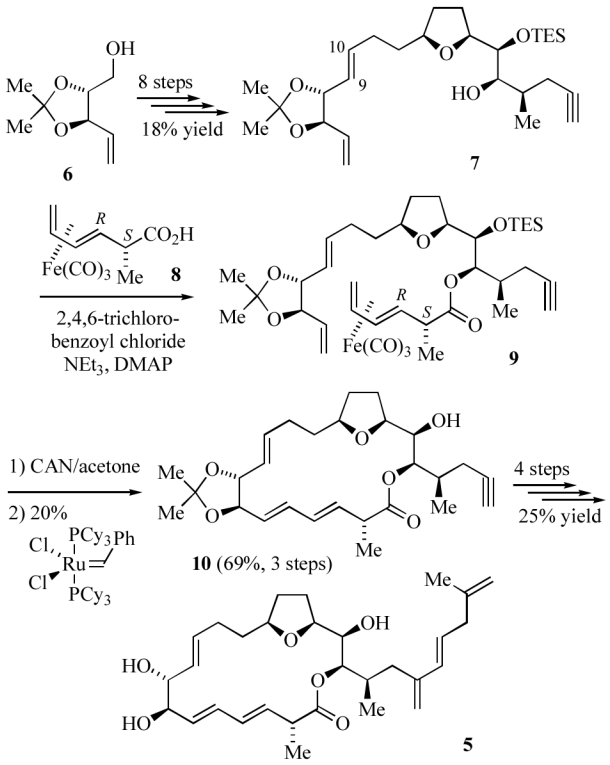

Scheme 1.
Synthesis of amphidinolide E.

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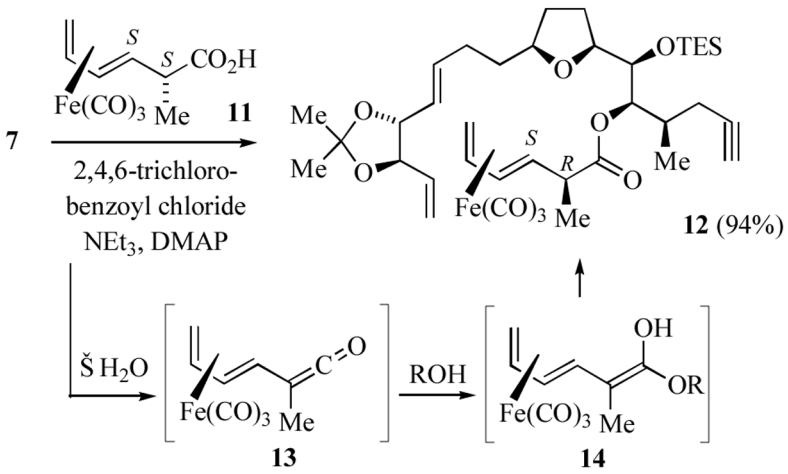

Scheme 2.
Esterification of (2*S*,3*S*)-(2-methyl-3,5-hexadienoic acid)$Fe(CO)_3$.

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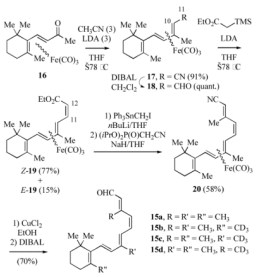

Scheme 3.
Stereoselective synthesis of 11*Z*-retinal via organoiron chemistry.

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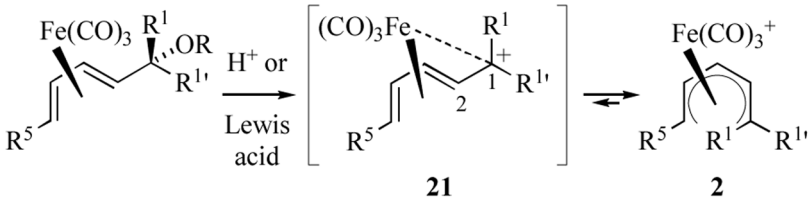

Scheme 4.
Preparation of acyclic (pentadienyl)iron cations.

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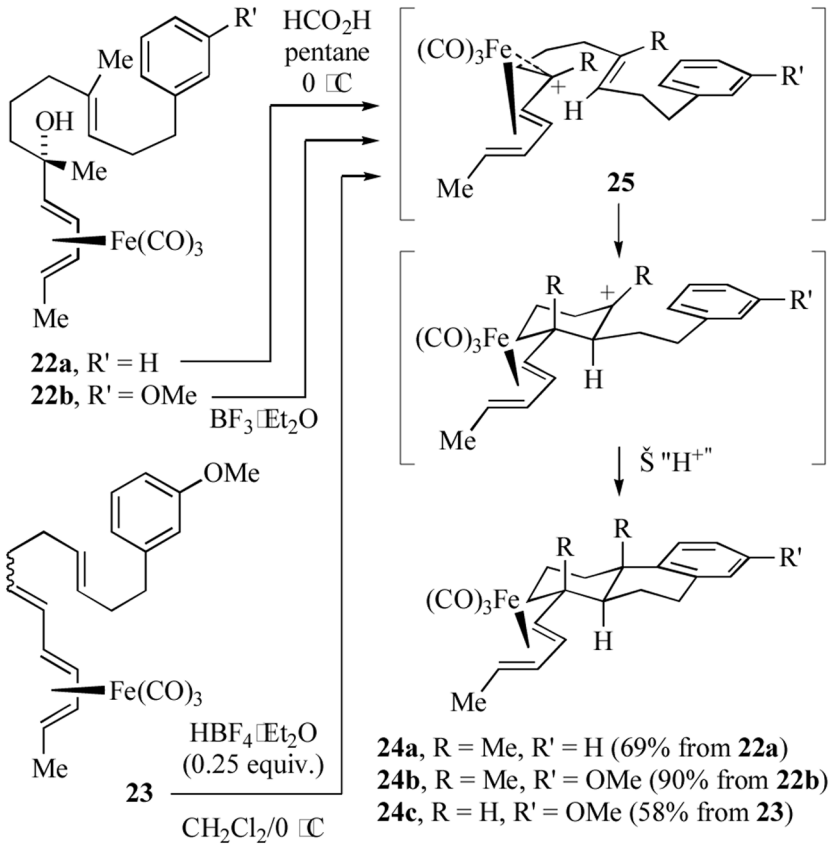

Scheme 5.
Polyene cyclizations initiated by a *trans* (pentadienyl)iron cation.

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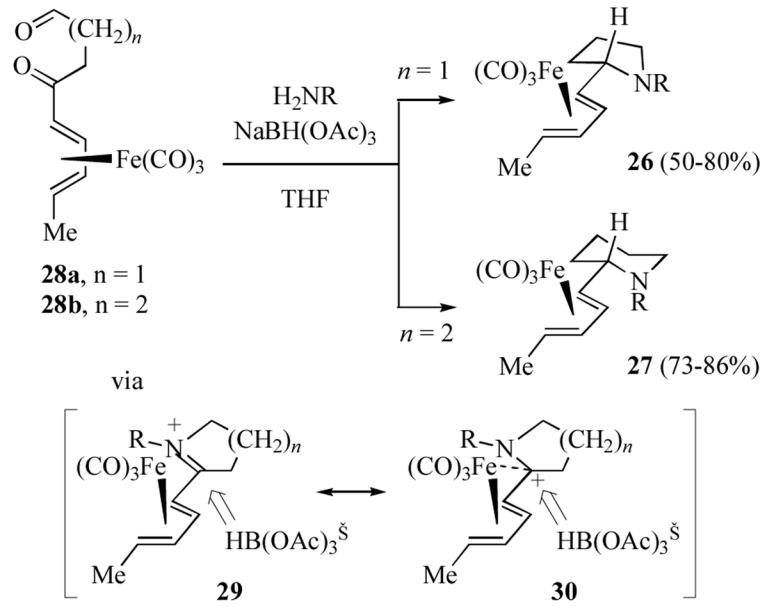

Scheme 6.
Reductive amination of diene ketoaldehyde complexes.

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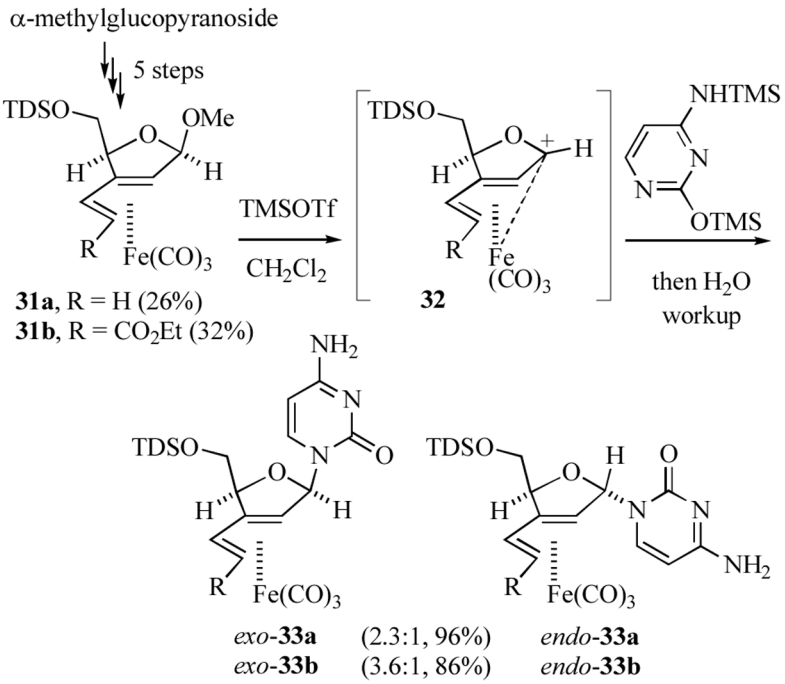

Scheme 7.
Preparation of organoiron nucleoside analogs (TDS = thexyldimethylsilyl).

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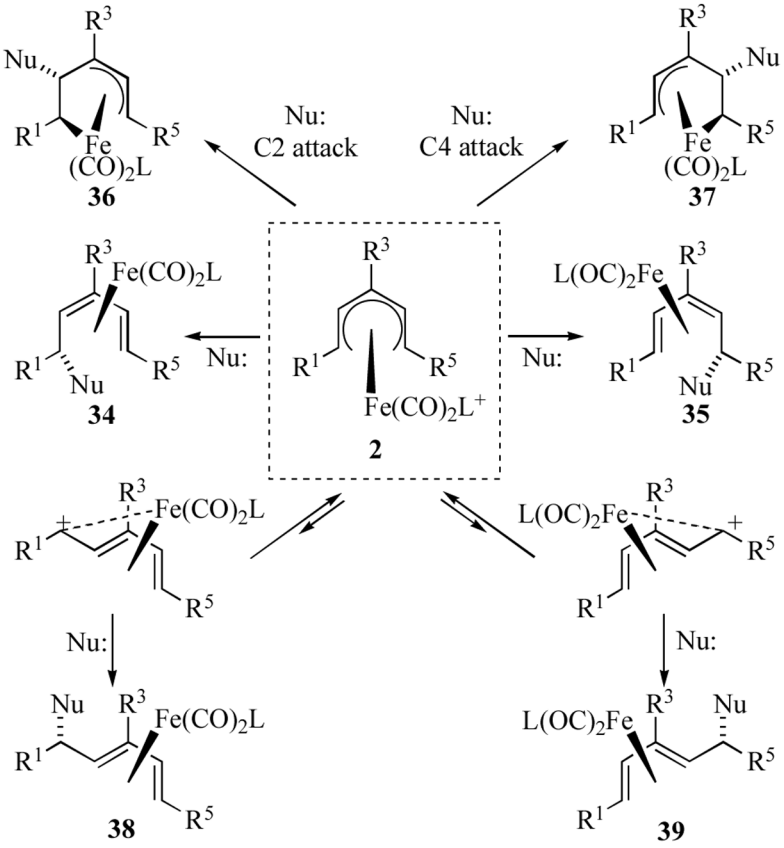

Scheme 8.
Modes of reactivity for isolable (pentadienyl)iron cations.

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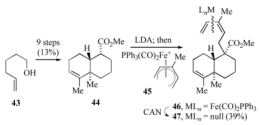

Scheme 9.
Synthesis of a 3-methyl-1,3*Z*-pentadienyl diterpene skeleton.

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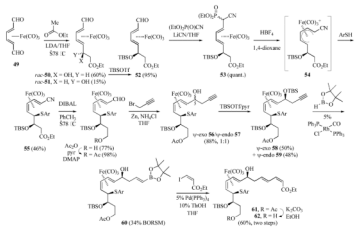

Scheme 10.
Takemoto synthesis of the C1–C15 segment of macrolactin A (Ar = *p*-FC_6H_4).

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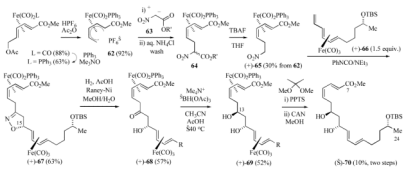

Scheme 11.

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

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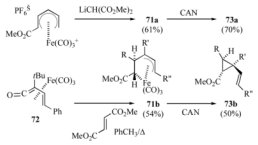

Scheme 12.

Synthesis of vinylcyclopropanes via oxidative decomplexation of (3-pentene-1,5-diyl)iron complexes (**a**, R = $CH(CO_2Me)_2$, R′ = R″ = H; **b**, R = CO_2Me, R′ = *t*Bu, R″ = Ph).

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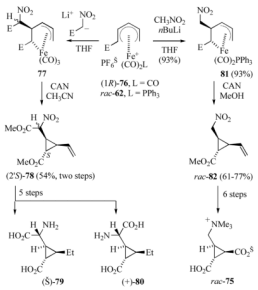

Scheme 13.
Synthesis of 2-(2′-carboxycyclopropyl)glycines and dysibetaine CPa (E = CO_2Me).

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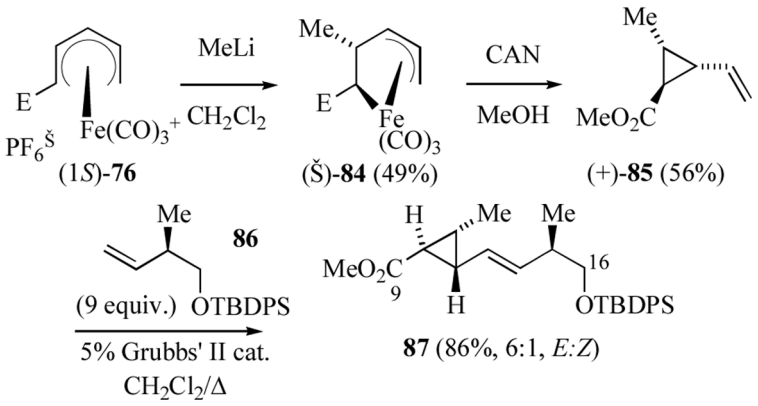

Scheme 14.
Synthesis of the C9–C16 segment of ambruticin (E = CO_2Me).

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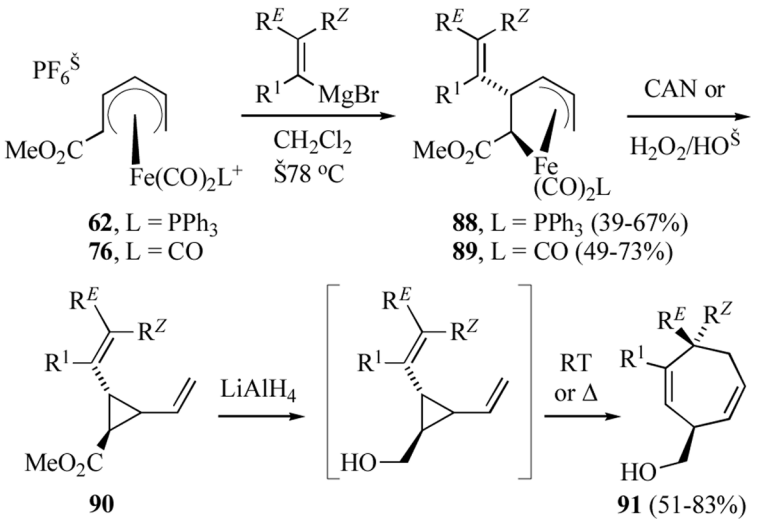

Scheme 15.
Synthesis of divinylcyclopropanes and Cope rearrangement.

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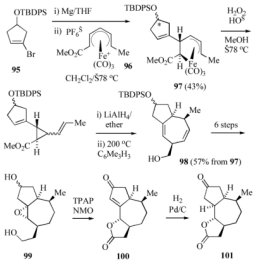

Scheme 16.
Preparation of the 5,7,5 ring system of the guianolides.

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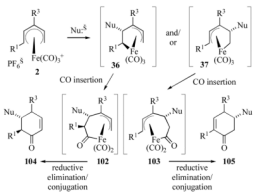

Scheme 17.
Generation of cyclohexenones from (pentadienyl)iron cations.

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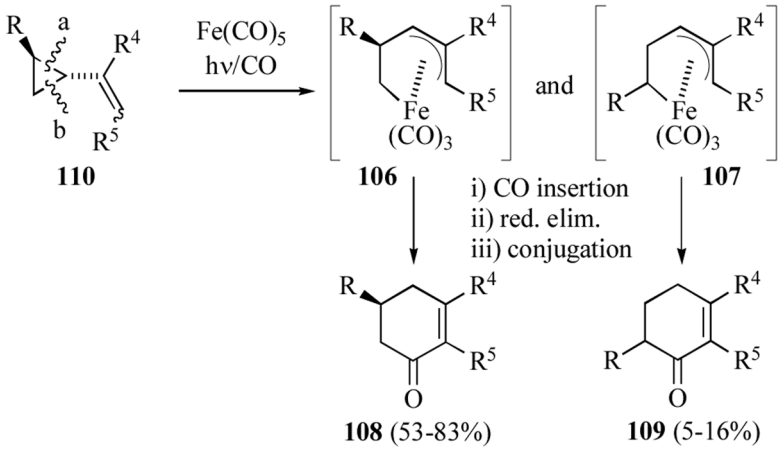

Scheme 18.
Generation of cyclohexenones via iron-mediated carbonylation of alkenylcyclopropanes.

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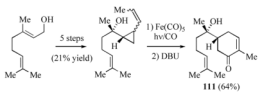

Scheme 19.
Taber and co-workers synthesis of (−)-delobanone.

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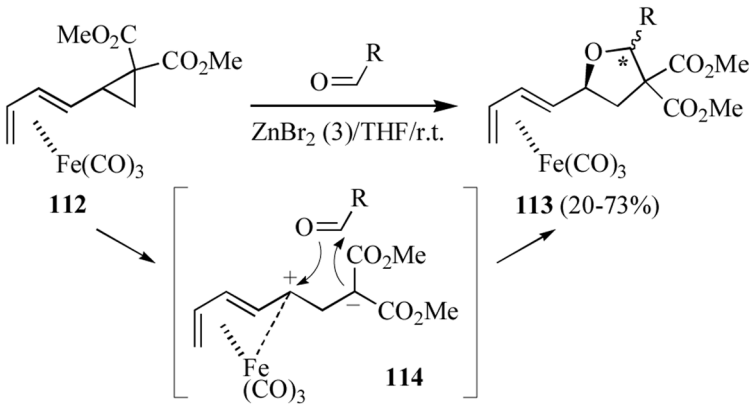

Scheme 20.
Formation of polysubstituted dienyltetrahydrofurans.

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