(π-Allyl)tricarbonyliron Lactone Complexes in Organic Synthesis: A Useful and Conceptually Unusual Route to Lactones and Lactams

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I. Introduction

The preparation and study of organometallic complexes has fascinated chemists for many years since the preparation of Zeise's salt in 1827.[1] The wealth of knowledge that has been generated has spawned new industries, owing to the exquisite properties and unique transformations that are possible with these species. Moreover the functional group tolerance and the potential for catalytic systems has revolutionized the way we design and conceive synthetic pathways toward organic molecules. The ever increasing demands from society for novel chemical entities with potent biological profiles or diverse functional properties continue to stimulate new science. As we move forward to the next century we can anticipate many exciting developments in chemical synthesis which will advance organic chemistry.

In this review we will concentrate on the chemistry of (π-allyl)tricarbonyliron lactone and lactam complexes, **1** and **2** (Figure 1), and their application to organic synthesis.[2] These architecturally interesting compounds, which are readily available from a variety of starting materials, provide a novel scaffolding which can be easily manipulated. Removal of the tricarbonyliron tether leads to a range of products including lactones, lactams, and masked dienylic alcohols. Control of stereoselectivity of reactions at functional groups in the side chains of these species is also readily achieved.[3]

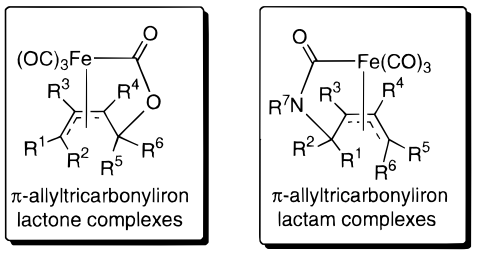

Figure 1.

A. General Properties and Structure

Before discussing their preparation and chemistry, it is pertinent to comment on the properties and the relevant structural features of these species. Most of the complexes which have been prepared to date are crystalline and may be obtained in their pure form by column chromatography on silica gel, Florisil, or alumina. They are quite stable in the solid state and may be stored under an inert atmosphere of argon for long periods of time without significant decomposition provided that light is excluded and the temperature kept below 4 °C. They are soluble in a wide variety of solvents including benzene, tetrahydrofuran, diethyl ether, dichloromethane, chloroform, and ethyl acetate and show little decomposition over typical reaction times of 1−24 h. If left in a solution of chloroform for several days at room temperature, however, appreciable decomposition of the complexes has been observed which we believe is due to the partial decomposition, in bright sunlight, of the solvent resulting in the production of hydrogen chloride and it is this which attacks the complexes and decomposes them. In bright sunlight under 1 atm of oxygen or by heating to greater than 40 °C in a variety of solvents, loss of carbon monoxide occurs leading to a variety of isolable and chemically useful decomposition products (see later for a more complete discussion). Consequently most reactions are carried out in the absence of light and under an inert atmosphere of argon.

The core (π-allyl)tricarbonyliron units of these complexes are relatively stable to a variety of reagents and conditions such as water, trimethylsilyl cyanide, *tert*-butylisonitrile, and a diverse range of oxidants including manganese(IV) oxide, copper(II)-chloride, iron(III) chloride, *tert*-butyl hydroperoxide, amine *N*-oxides, chromium trioxide, pyridinium chlorochromate, pyridinium dichromate, ozone, and activated dimethyl sulfoxide. They are also stable to dilute acid, triethylamine, catalytic hydrogenation, Wittig reagents, the Tebbe reagent, samarium(II)

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Graham Meek was born in Leicester, England, in 1971. He received his B.A.(Hons.) in Natural Sciences from the University of Cambridge in 1992 and studied for his Ph.D. with Steven Ley working on (π-allyl)tricarbonyliron lactone complexes. He is currently carrying out postdoctoral studies with Mark Lautens at the University of Toronto.

iodide, and Lewis acidic organometallic reagents. Consequently, the stability toward these reagents allows for extensive chemistry to be performed on the side chains prior to decomplexation although other more vigorous reagents do cause damage to the π-allyl unit of these complexes. In certain cases, characterizable products are produced upon exposure to concentrated acids, Lewis basic organometallics, sodium borohydride, lithium aluminum hydride, sodium hydride, heat, aqueous base, ceric ammonium nitrate, carbon monoxide, amines in association with Lewis acids, triphenylphosphine, and Meerwein's reagent. These will be discussed in more detail later.

Liam R. Cox received a B.A.(Hons.) in Natural Sciences from the University of Cambridge in 1994 and is presently working toward a Ph.D. with Steven Ley.

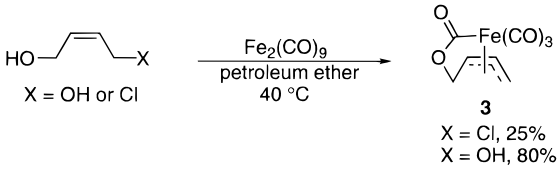
The presence of the templating iron atom has significant effects on the reactivity of these compounds and this is reflected in their spectroscopic properties. The lactone carbonyl group, for instance, absorbs in the infra red region at typically 1635−1655 cm^{-1}, whereas the amide carbonyl in the lactam complexes is found around 1580−1600 cm^{-1}. The low stretching frequencies of these units is consistent with their low reactivity toward nucleophilic reagents.

There are also large chemical shift differences in the ^1H NMR spectra of these complexes. In the lactone complexes **1**, for example, where R^1 is hydrogen a resonance for this proton is observed at δ 3.3−3.9 ppm, whereas the inner proton R^2 is shifted to δ 2.6−3.1 ppm as a result of being closer to the iron atom. Similar, although less pronounced, shifts are noticed for methyl groups placed at these positions. One should be cautious, however, in using the published literature data since misassignments have been made and large solvent shift changes can occur when spectra are obtained in halogenated solvents as opposed to benzene-d^6. Interestingly, from X-ray crystal structures of these complexes it is apparent that the hybridization at the terminii of the complexing η^3-allyl unit is between sp^2 and sp^3.

II. (π-Allyl)tricarbonyliron Lactone Complexes

The first reports of these complexes appeared in the literature in 1964. Murdoch noted that but-2-ene-1,4-diol or 4-chlorobut-2-en-1-ol reacted with diiron nonacarbonyl to give the corresponding (π-allyl)tricarbonyliron lactone complex **3**[4] (Scheme 1).

Scheme 1

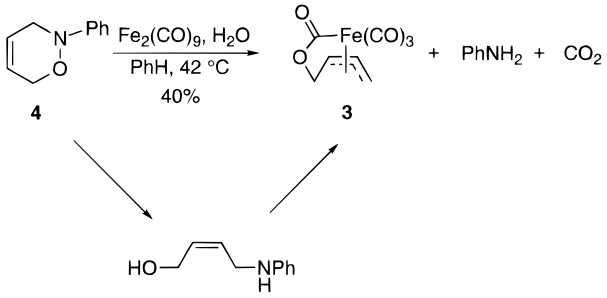


Other simple lactone complexes were prepared using these methods in poor yields ranging from 1 to 78%, the latter result being observed in one isolated case. Heck simultaneously reported the reaction of *cis*-4-chlorobut-2-en-1-ol with iron pen-

tacarbonyl in dichloromethane, under irradiation conditions, to afford **3** but in very low yield (5%).[5]

It was not until 10 years later that interest in these compounds was renewed when Shvo observed[6] that oxazines, such as **4**, reacted with diiron nonacarbonyl in the presence of water and benzene to give the same complex **3** in 40% yield (Scheme 2). It was shown

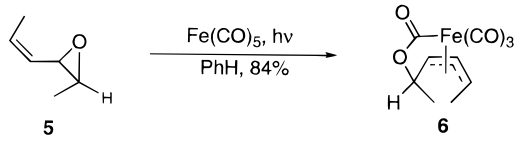
Scheme 2



that diiron nonacarbonyl mediated reduction of the oxazine **4** to *cis*-4-(phenylamino)but-2-en-1-ol which subsequently underwent reaction with diiron nonacarbonyl to produce **3** in a preparatively useful yield of 78%.

The next important advance in the story occurred when Aumann showed that (π-allyl)tricarbonyliron lactone complexes could be obtained more conveniently by subjecting alkenyl epoxides to irradiation through a Duran filter in the presence of iron pentacarbonyl in benzene.[7] In this way four lactone complexes were synthesized in yields ranging from 48 to 90%. The use of these procedures was further investigated by Moriarty who suggested that the reaction proceeded with complete stereoselectivity[8] in that the epoxide **5**, for example, reacted to give the lactone complex **6** as the only reported product (Scheme 3). We and Aumann, however, have ex-

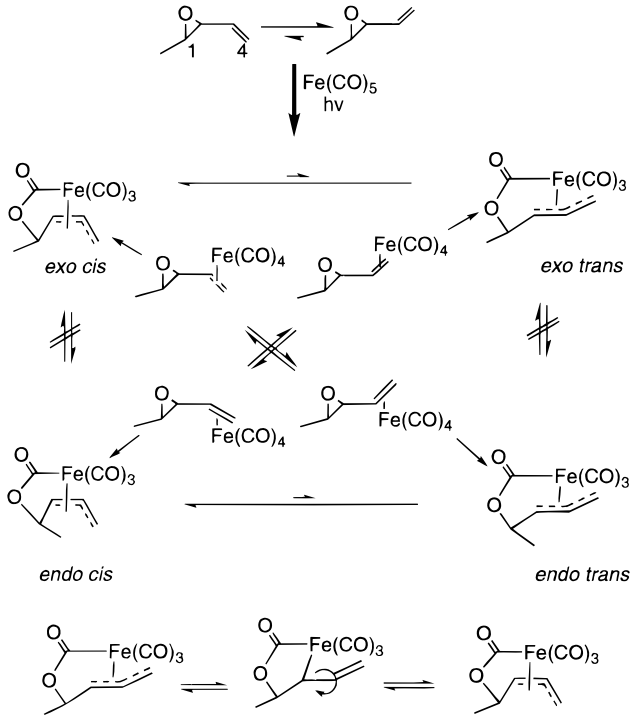
Scheme 3



amples which would suggest that the reactions are less stereoselective than indicated by this early Moriarty work.

In a detailed study of the mechanism of the reaction of alkenyl epoxides with iron pentacarbonyl under irradiation conditions, Aumann demonstrated[9] that the first step involves complexation of the coordinatively unsaturated tetracarbonyliron, which is generated *in situ* by ejection of one molecule of carbon monoxide, with the alkene bond from either stereoface. This gives rise to four possible diastereoisomeric intermediates which undergo subsequent insertion of carbon monoxide into the oxirane ring to form the iron complexes. Rapid isomerization prior to this insertion may account for the formation of only the *cis* complexes in the majority of cases (see later for exceptions). However even if the thermodynamically less stable *trans* complex is formed, then its interconversion to the more stable *cis* product is readily achieved via a pathway involving a σ-bonded intermediate (Scheme 4). The *trans* products are

Scheme 4

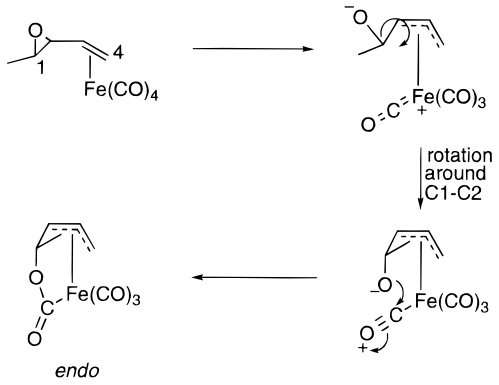


only observed when C1 is disubstituted suggesting that in all other cases the equilibria heavily favor the direction of those intermediates that give rise to the *cis* complexes (Scheme 4).

It is also clear that epoxides which are unsymmetrically substituted at C1 give rise to a mixture of diastereoisomeric (π-allyl)tricarbonyliron lactone complexes. In the majority of cases, however, the predominant stereoisomer formed is that in which inversion of configuration at C1 has occurred (the diastereoisomers are designated *endo* or *exo* according to whether the dominant substituent at C1 points toward, or from, the iron atom, respectively). The proposed mechanism can account for this observation by directing the equilibrium between the tetracarbonyliron species to favor that in which the less hindered face of the double bond is bound to the coordinatively unsaturated iron species. This is consistent with the iron moiety being a "soft" electrophile[10] so that the steric effects of the oxygen outweigh any electronic effects which might attract the iron to the same face of the double bond as the epoxide. The inversion of configuration at C1 is consistent with the necessity of bond rotation around C1−C2, which is required if the lactone linkage is to be formed from the *anti* intermediate (Scheme 5). However the results on which this mechanism is based do not exclude alternative pathways, such as those involving primary coordination with the oxygen of the epoxide. The ensuing intermediate would, however, be of much higher energy owing to the lack of metal-based stabilization of the allylic cation that would be created.

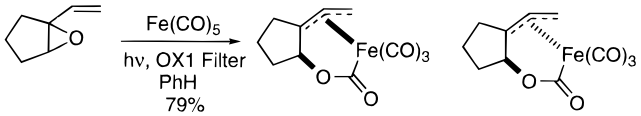
Our group first became interested in these tricarbonyliron complexes as potential precursors in organic synthesis when we reasoned that upon decomplexation they could afford a new route to lactones.[2] This is indeed true and will be discussed in detail later. In a continuation of these early studies we also

Scheme 5



showed[11] that alkenyl epoxides such as **7** can afford two isomeric lactone complexes **8** and **9** in which the tricarbonyliron moiety is complexed to the allyl unit on the same face, *syn* **8**, or opposite face, *anti* **9**, relative to the oxygen substituent (Scheme 6). More

Scheme 6



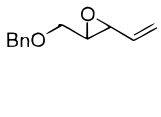
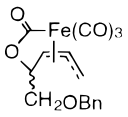
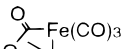
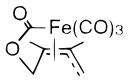
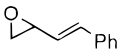
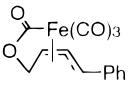
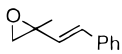
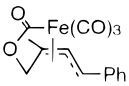
7 **8** *syn* **9** *anti*

6 : 1

importantly, however, is that they lead to different ratios of lactonic products upon oxidative decomplexation (see later).

Although the required complexes could be produced by these methods we sought alternative sequences that would be more convenient and useful on a larger scale. In particular the use of iron pentacarbonyl is less appealing, owing to the volatile and toxic nature of this reagent. Moreover, the use of irradiation often requires the use of dilute solutions and the choice of benzene as solvent is not ideal. Thermal reactions, likewise, are not acceptable if sensitive substrates are required. For these reasons we devised alternative reaction conditions that were practically more useful. The first of these arose from observations that the crystalline and involatile diiron nonacarbonyl dissociated in tetrahydrofuran, THF, to give a red solution thought to contain $Fe(CO)_4$·THF.[12] We envisaged that the weakly ligated tetrahydrofuran molecule would be easily displaced by the double bond of the alkenyl epoxide and subsequently form the (π-allyl)tricarbonyliron lactone complexes as described above. In practice the reaction of 2.5 equiv of diiron nonacarbonyl in tetrahydrofuran with alkenyl epoxides proceeds well to give the corresponding (π-allyl)tricarbonyliron lactone complexes,[13] and this is now our method of choice for the preparation of these compounds. (Note that iron pentacarbonyl remains a byproduct of the reaction and the usual care must be taken particularly in the purification and isolation steps.) The end point of the reaction is also easily monitored in that the excess tetracarbonyliron formed readily undergoes trimerization to give green triiron dodecacarbonyl, which is unreactive.

Table 1

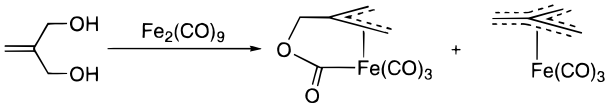
vinyl epoxide	lactone complex	method	yield (%)
		A B	34 79
		A B	94 76
		A B	42 44
		A B	100 68
		A B	64 63

method A: $Fe_2(CO)_9$, THF, RT
method B: $Fe_2(CO)_9$, PhH, sonication, RT

A complimentary route to this procedure, which we have developed[13] and which has proven to be useful in circumstances where the yields are lower using the previous methods, involves the requisite breakdown of diiron nonacarbonyl to the reactive, coordinatively unsaturated tetracarbonyliron species by using ultrasonic techniques. Under these conditions it is necessary to use hydrocarbon solvents such as benzene or petroleum ethers in which diiron nonacarbonyl is insoluble. Again an excess of diiron nonacarbonyl is used (typically 2.5 equiv). In Table 1 are listed some of the comparative examples of these new methods leading to tricarbonyliron lactone complexes.

The type of ultrasound generator used in the reactions varies from the simple 80 W 55 kHz cleaning bath to the use of 850 W Heat Systems Ultrasonics Inc. sonicator if the reactions are especially sluggish. Nevertheless these conditions are attractive as they occur at ambient temperature and multigram preparation of the complexes can be achieved very readily. There are, however, cases where different product ratios may be observed when the different methods of preparation are employed. The reaction of the alkenediol **10**, for example, with excess diiron nonacarbonyl, either in tetrahydrofuran or using ultrasound, produces the tricarbonyliron lactone complex **11** together with significant quantities of trimethylenemethane species **12**[14] (Scheme 7). Spontaneous loss of carbon dioxide from the presumed lactone complex intermediates to give trimethylenemethane derivatives has also been noticed under photochemical conditions when allenes are reacted with aldehydes in the presence of iron pentacarbonyl.[15]

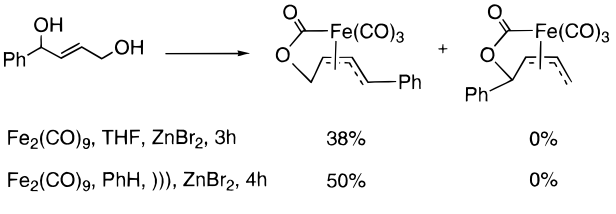
Scheme 7



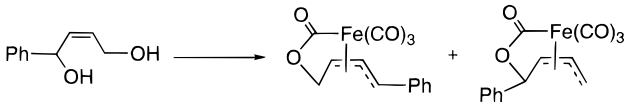
10		11	12
	THF, RT	12%	63%
	))), PhH, RT	58%	5%

The volatility and potential toxicity of some alkenyl epoxides makes them less than ideal candidates for the preparation of these complexes. Consequently, we have also investigated alternative precursors for the formation of these organometallic species. In the first of these, we have shown that *cis*- or *trans*-but-2-ene-1,4-diols are reasonable substrates for complex formation[14] despite the previous observations where very low yields were obtained. In Scheme 8 are

Scheme 8



$Fe_2(CO)_9$, THF, $ZnBr_2$, 3h	38%	0%
$Fe_2(CO)_9$, PhH,))), $ZnBr_2$, 4h	50%	0%

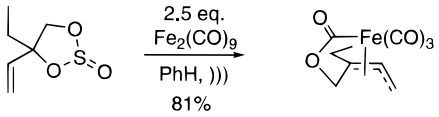


$Fe_2(CO)_9$, THF, $ZnBr_2$, 3h	32%	47%
$Fe_2(CO)_9$, PhH,))), $ZnBr_2$, 3h	22%	37%

illustrated some examples of these procedures although the reader is advised to consult the work for a much more detailed discussion and to see other examples of the process.

Finally, we have developed a route to (π-allyl)tricarbonyliron lactone complexes which utilizes alkenyl 1,2-cyclic sulfites as precursors.[16] These were chosen as starting materials as they would be nonvolatile alternatives to alkenyl epoxides.[17] Moreover these could be prepared from 1,2-diols which, in principle, are readily obtained from alkenes by glycolation possibly using current asymmetric procedures[18] to give enantiomerically enriched complexes. Although several examples were investigated the conversion of the sulfite **13** to the lactone complex **14** by the diiron nonacarbonyl/ultrasound method illustrates the process (Scheme 9).

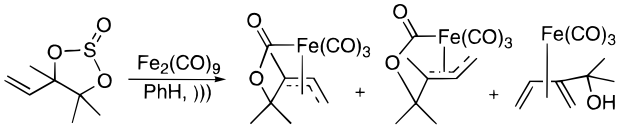
Scheme 9



13 **14**

With very hindered cyclic sulfites other products are also observed. The diol sulfite **15**, for example, gives a mixture of the (π-allyl)tricarbonyliron complexes **16** and **17** together with the (η^4-diene)tricarbonyliron complex **18** (Scheme 10). These methods are particularly recommended when the precursors

Scheme 10



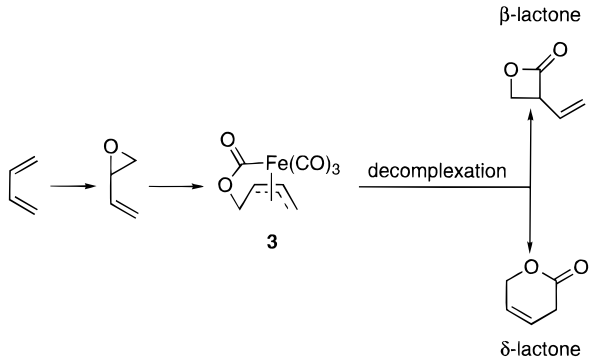
15	16	17	18
	28%	28%	44%

are low molecular weight materials which otherwise would be very volatile if one started with the corresponding alkenyl epoxide.

A. Synthesis of Lactones

In 1977 we showed for the first time that (π-allyl)tricarbonyliron lactone complexes were novel precursors for lactone synthesis.[19] We reasoned that decomplexation could lead to carbon−carbon coupling of the iron acyl carbon with either terminus of the allyl unit affording either a β- or a δ-lactone (Scheme 11). Overall this pathway would constitute an in-

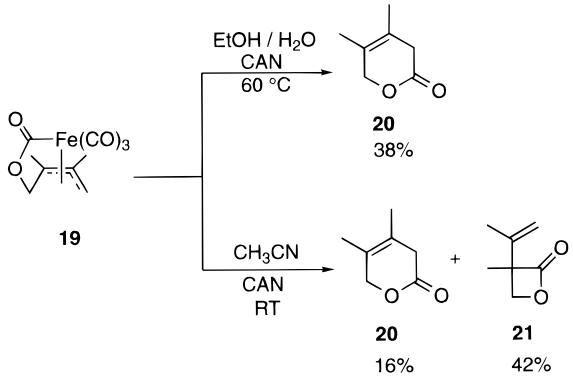
Scheme 11



corporation of a carbon dioxide unit to a diene which would be an unusual method of synthesis of these potentially useful systems.

In our early experiments[20] we found that the dimethyl lactone complex **19** underwent oxidative decomplexation with ceric ammonium nitrate, CAN, in aqueous ethanol to produce the δ-lactone **20** in 38% yield. However, using acetonitrile as solvent at room temperature, the major product was the β-lactone **21** obtained in 42% yield (Scheme 12).

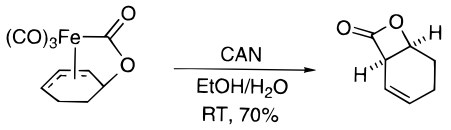
Scheme 12



When the bridged complex **22** was oxidized at room temperature with ceric ammonium nitrate, a single

β-lactone product **23** was isolated in 70% yield (Scheme 13).

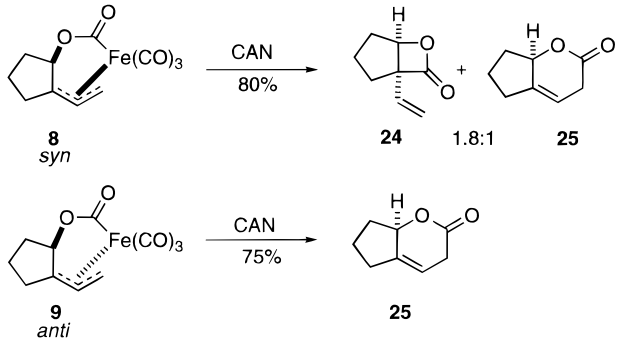
Scheme 13



22 **23**

Indeed this trend for the formation of the small-ring β-lactone proved to be general unless special constraints were imposed. When the previously described cyclopentyl (π-allyl)tricarbonyliron lactone complexes **8** and **9**, for example, were separately oxidized different product ratios were obtained[20] (Scheme 14). With the *syn* derivative, **8**, the major

Scheme 14



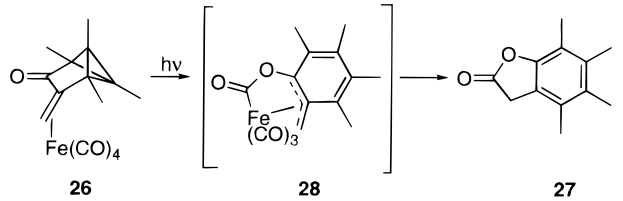
8 *syn* **24** 1.8:1 **25**

9 *anti* **25**

product was the β-lactone **24** together with the δ-lactone **25**. With the *anti* compound, **9**, however, the sole product was the δ-lactone **25**. The formation of a corresponding β-lactone in this latter case was presumably precluded by ring strain in the formation of a *trans*-fused product.

Irradiation of the η^2 tetracarbonyliron complex **26** has also been shown[21] to give the five-membered ring lactone **27**. This reaction is believed to proceed through the intermediate (π-allyl)tricarbonyliron lactone complex **28** (Scheme 15).

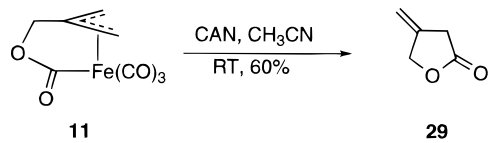
Scheme 15



26 **28** **27**

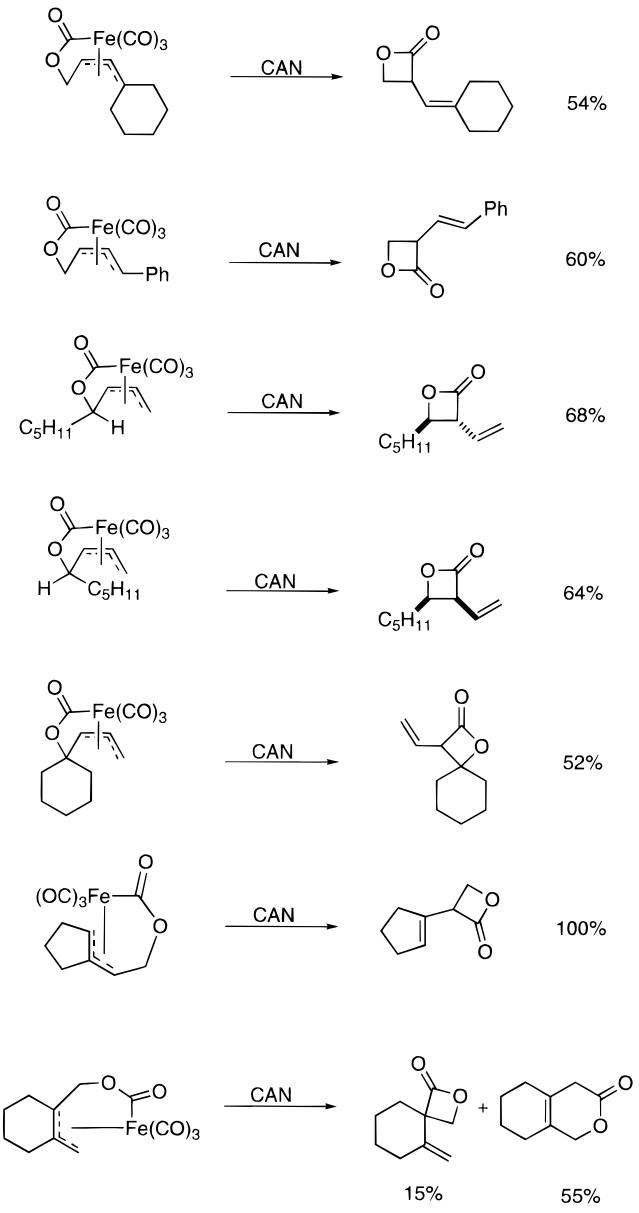
Five-membered ring lactones are also obtained from oxidation of the bridged (π-allyl)tricarbonyliron complex[22] **11** described earlier. In this case the β-methylene lactone **29** is formed in good yield using ceric ammonium nitrate as the decomplexing oxidant (Scheme 16).

Scheme 16



11 **29**

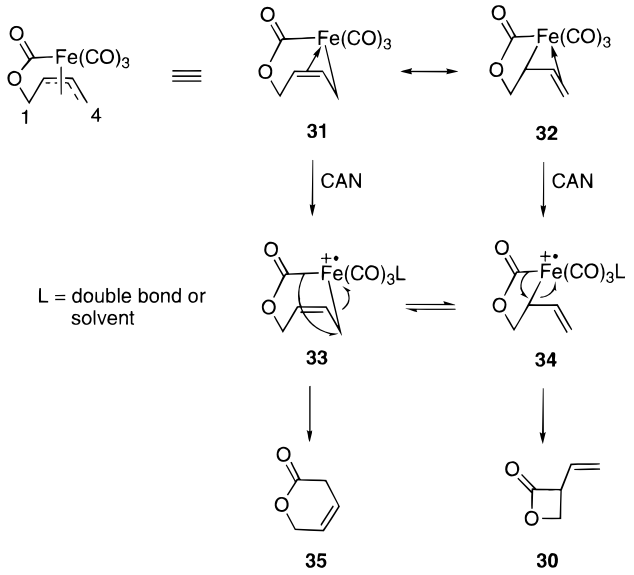
Scheme 17



In the full paper[20] which describes our work on the treatment of (π-allyl)tricarbonyliron lactone complexes with ceric ammonium nitrate, several other β-lactones have been prepared which clearly illustrate the generality of this process. For maximum reproducibility of reactions and yields, sonolytic activation of CAN prior to the addition of the complex is necessary. Optimum selectivity is observed at temperatures between −10 °C and −5 °C. For solubility reasons polar solvents such as acetonitrile, methanol, and ethanol are usually the solvents of choice. Some of the better results of these experiments are listed in Scheme 17 although the reader is advised to consult the literature for more examples of this process. Of paramount importance for the application of this chemistry is the stereospecific nature of the decomplexation reaction: the stereochemistry around the allyl unit is preserved in the product lactone. This aspect has allowed for the stereodefined synthesis of a number of biologically interesting natural products which contain a β-lactone (see later).

The proposed mechanism[20] of the ceric ammonium nitrate decomplexation accounts for the dominance of the β-lactone, **30**, as product and the stereospecificity. It also explains the observation that substitution at C2 leads to a poorer selectivity for the β-lactone. These (π-allyl)tricarbonyliron lactone complexes can be represented by the two canonical forms **31** and **32** (Scheme 18). Upon one-electron oxidation

Scheme 18



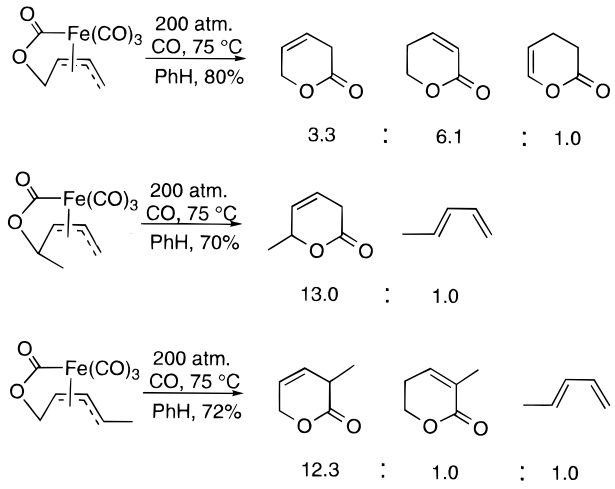
by ceric ammonium nitrate an equilibrating mixture of the radical cationic intermediates **33** and **34** is formed. Reductive elimination of **34** leads to the β-lactone while collapse of **33** results in the δ-lactone, **35**. If **34** reductively eliminates more rapidly than **33** then the β-lactone will dominate. Hence, the selectivity for the formation of the smaller ring lactone appears to be under kinetic control. The concerted nature of the reductive elimination step accounts for the stereospecific nature of the reaction.

Inspection of **33** and **34** reveals that substitution at C2 destabilizes the five-membered ring in **34**, due to steric interactions with the bulky tricarbonyliron moiety, with respect to the seven-membered ring present in **33**. Hence, the equilibrium favors **33** and the preference for the smaller ring lactone is diminished.

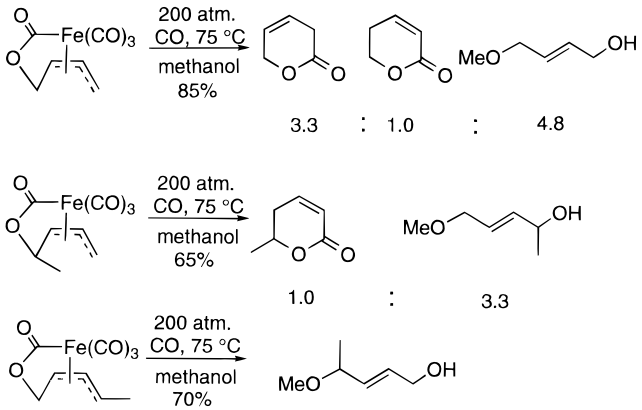
Complementary to the oxidative decomplexation of (π-allyl)tricarbonyliron lactone complexes, Aumann has shown that these species can be exhaustively carbonylated between 75−115 °C and 220−300 atm of carbon monoxide to selectively afford δ-lactones.[9] Listed below are three representative examples of this process using benzene (Scheme 19) or methanol (Scheme 20) as the solvent. What should be noticed from these results, and the five other comparative examples studied, is that mixtures of unsaturated δ-lactones are often produced and in methanol, addition products are also present, sometimes to the exclusion of the lactones.

From a synthetic point of view therefore, these reactions are useful when δ-lactones are required in which the position of the double bond in the product is unimportant, for example if the next step in the synthesis involves hydrogenation to remove the

Scheme 19



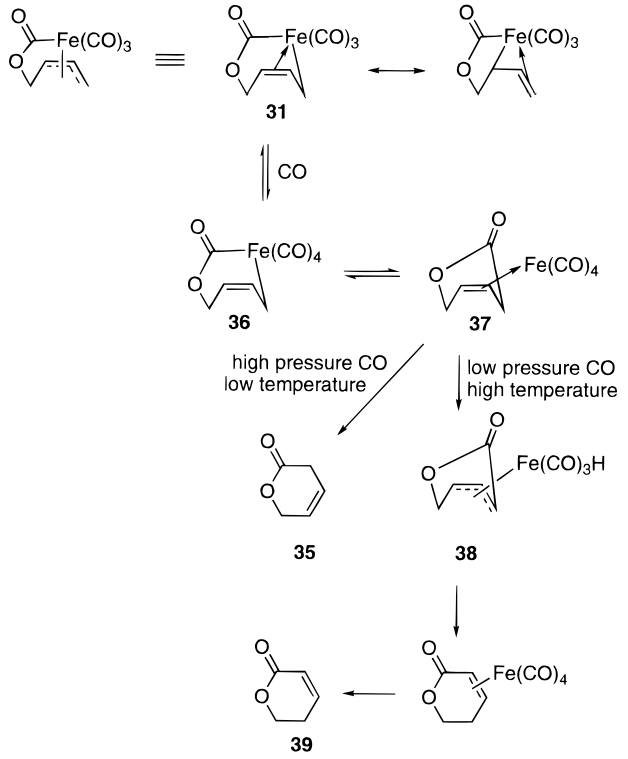
Scheme 20



double bonds. If, however, selective placement of the double bond at the α,β or β,γ positions is necessary, modified reaction conditions are required.[23] We find that if the reaction is run under high pressures of carbon monoxide at temperatures lower than 55 °C in the presence of a tetracarbonyliron scavenger, such as acrolein, the major product is the β,γ-unsaturated δ-lactone. In contrast, at higher temperatures under longer reaction times and in the absence of scavengers, the α,β-unsaturated δ-lactone is the preferred product.

Mechanistically this reaction can be viewed as proceeding as shown in Scheme 21.[23] Substitution at the iron center in the canonical form **31** of the η^2-bound olefin ligand for a molecule of carbon monoxide affords **36**. Reductive elimination and consequent reformation of the olefin−Fe bond (necessary to maintain an 18-electron species) results in the pivotal intermediate **37**, which under conditions of low temperature and high pressure releases the β,γ-unsaturated δ-lactone **35**. Under low pressure carbon monoxide and high temperature the desire for ligand exchange with carbon monoxide with the concomitant release of the organic fragment is diminished, and instead isomerization of the double bond occurs. Presumably, this proceeds via the tricarbonylhydrido species **38** which following isomerization releases the thermodynamically more stable α,β-unsaturated δ-lactone **39** after ligand exchange with a molecule of carbon monoxide.

Scheme 21



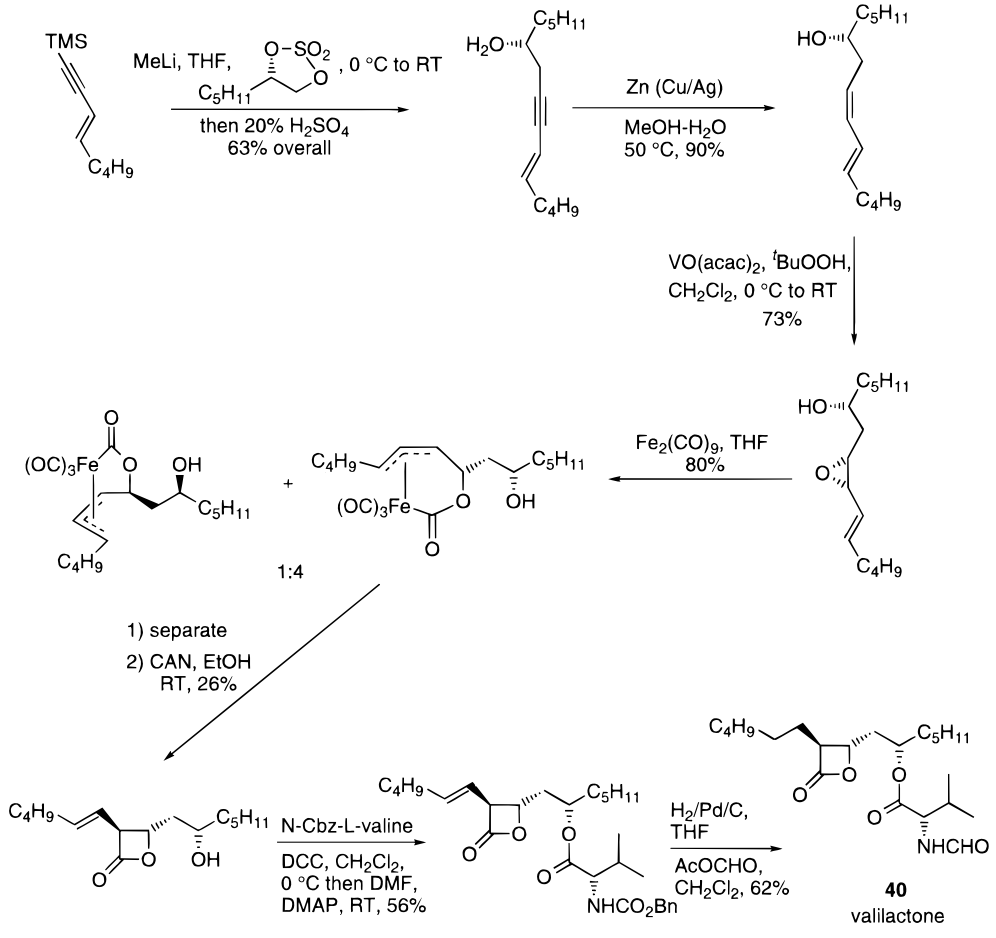
B. Natural Product Synthesis

In order to assess the viability of any new synthetic method it is commonplace to challenge the method by application to the synthesis of complex molecules. Biologically active natural products are therefore often chosen as targets for synthesis since they usually contain a range of functionalities which require stereoselective incorporation. In view of the previous results where it is possible to convert (π-allyl)tricarbonyliron lactone complexes to small-ring β-lactones, application to natural product synthesis is of interest. Currently there is considerable activity concerning a number of β-lactones of natural origin which have been shown to have useful biological properties.[24]

One of these compounds is the molecule valilactone (**40**) which was isolated from *Streptomyces albolongus* and shown to be a potent esterase inhibitor.[25] Embedded in this molecule is a *trans*-substituted β-lactone which could, in principle, arise from an appropriately substituted (π-allyl)tricarbonyliron lactone complex by oxidation with ceric ammonium nitrate. This plan was successful and led to the first enantioselective total synthesis[26] of valilactone (**40**), which is delineated in Scheme 22.

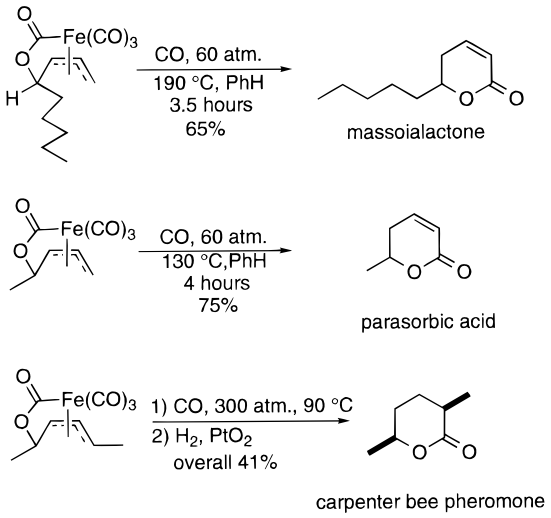
δ-Lactone natural products, both saturated and unsaturated, are also very common. Similarly many of these compounds display biological properties and in the past, many routes to these compounds have been developed. A conceptually new way to these systems which we chose to investigate was the exhaustive decarbonylation pathway from appropriately functionalized (π-allyl)tricarbonyliron lactone complexes.

Scheme 22



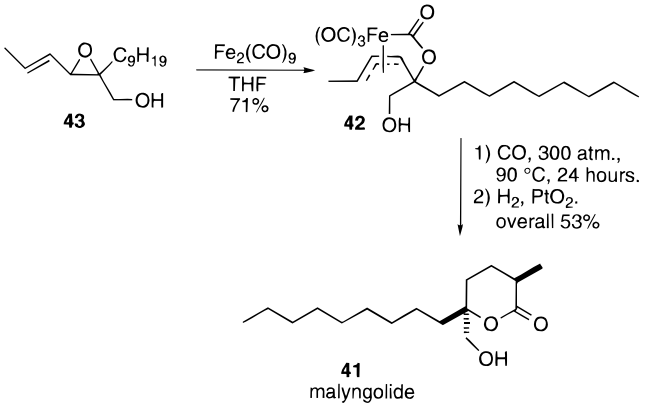
The racemic syntheses of three simple natural product lactones,[27] massoialactone, parasorbic acid, and the carpenter bee pheromone are shown in Scheme 23 commencing from the appropriate (π-allyl)tricarbonyliron lactone complexes.

Scheme 23



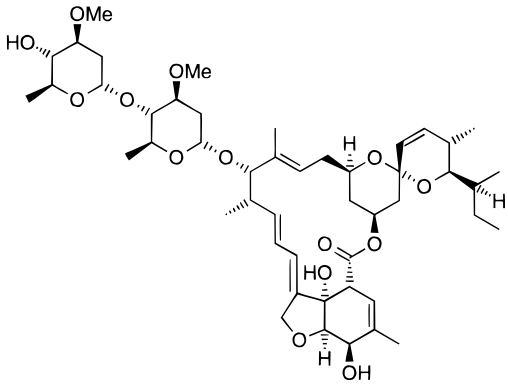
We have also used these methods to achieve the racemic synthesis of a more functionalized δ-lactone natural product, malyngolide (**41**).[27] This compound, which was isolated from a Hawaiian marine blue-green algae, *Lyngbya majuscula*, has mild antibiotic properties.[28] The synthesis of **41** is once again straightforward and makes use of the formation of the tricarbonyliron lactone complex **42** prepared from the appropriately substituted epoxide **43**. Exhaustive carbonylation followed by hydrogenation affords the target molecule in reasonable overall yield (Scheme 24). This route is still reasonably concise

Scheme 24



and compares well with other syntheses.[29] Moreover, it should be noticed that no protection of the alcohol was necessary throughout the sequence.

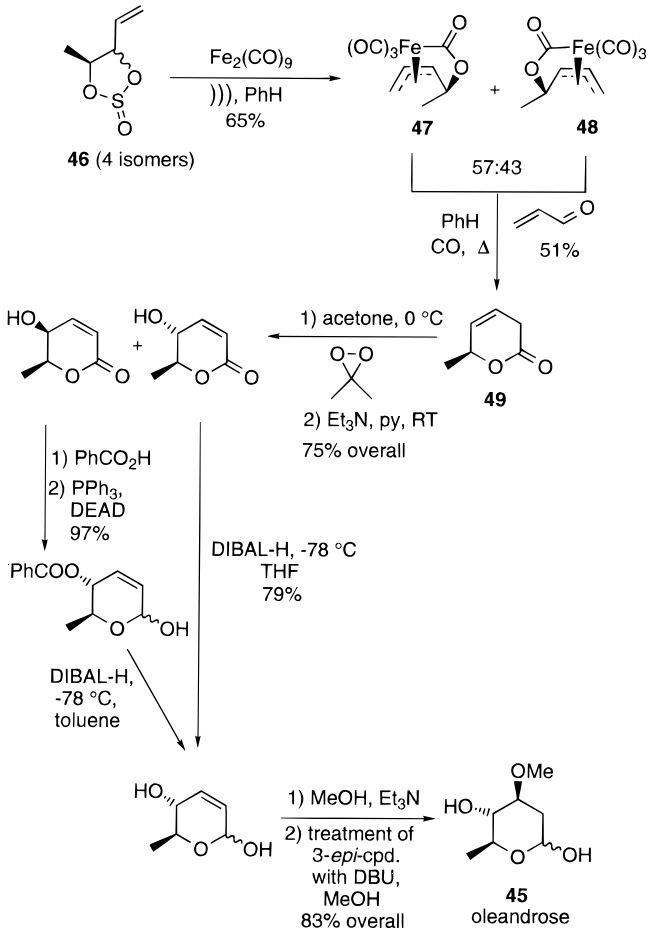
In addition to these studies we have also investigated the preparation of various substituted δ-lactones as building blocks for more complex natural product syntheses. One of the more complicated of these programs involved the enantioselective total synthesis of avermectin B1a (**44**).[30] This compound has attracted enormous attention owing to its extraordinarily potent antiparasitic activity.[31] Our route to **44** recognized the opportunity to use (π-allyl)-tricarbonyliron lactone complexes for the construction of both the appending bis-oleandrose sugar component and the formation of the inherent spiroketal moiety.



44
avermectin B1a

For the enantioselective synthesis of oleandrose (**45**), a 2-deoxy sugar, a short route was developed from an alkenyl-substituted cyclic sulfite **46** which upon reaction with diiron nonacarbonyl, under ultrasonic conditions, furnished the corresponding diastereoisomeric tricarbonyliron complexes **47** and **48**. Although these could be separated, it was found that exhaustive carbonylation of both species, in the

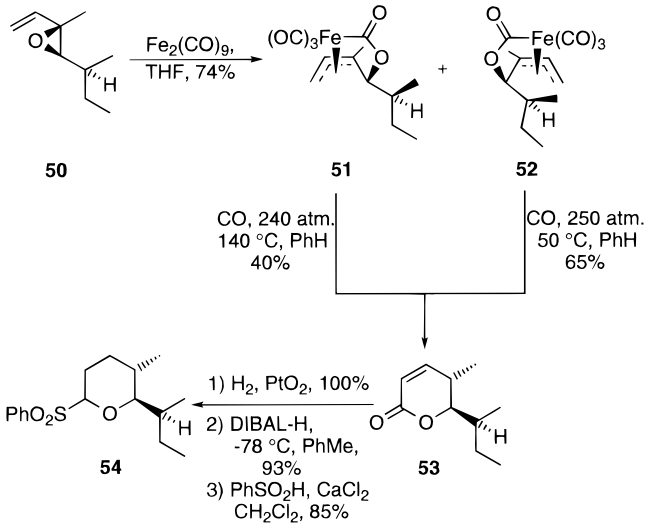
Scheme 25



presence of an iron tetracarbonyl scavenger (acrolein), resulted in the β,γ-unsaturated lactone **49** being obtained in reasonable yield. This was then processed to oleandrose via a convergent route (Scheme 25).[32]

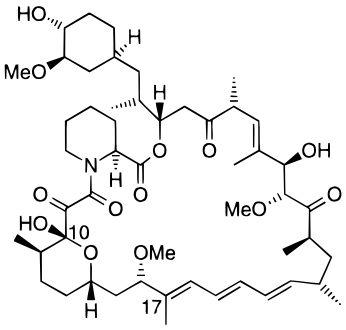
The northern hemisphere spiroketal fragment of avermectin B1a was obtained as follows.[33] Treatment of the homochiral epoxide **50** with diiron nonacarbonyl in tetrahydrofuran gave a 1:1 mixture of the corresponding tricarbonyliron lactone complexes, **51** and **52**, in 74% overall yield. These were separated, and each was converted to the same α,β-unsaturated δ-lactone **53** by exhaustive carbonylation. This carbonylation was deliberately carried out such that double bond migration occurred under equilibrating conditions to give the more stable pseudo-diequatorially substituted lactone. This lactone was then processed to the sulfone **54** by standard reactions (Scheme 26).

Scheme 26



As we knew, from previously established methodology developed within our group, that sulfones such as **54** are excellent precursors of spiroketals,[34] this material was readily transformed into **55** (Scheme 27) which was eventually processed into the natural product **34**.

We have also used the iron carbonyl methodology for the preparation[35] of a key lactone fragment **56** necessary for our projected synthesis[36] of the immune suppressive agent rapamycin (**57**).



57

rapamycin

The C10−C17 unit **56** was obtained following a standard protocol from the alkenyl epoxide **58**, in which the necessary stereochemistry was installed by application of the catalytic Sharpless asymmetric epoxidation.[37] This epoxide **58** was converted to the corresponding (π-allyl)tricarbonyliron lactone complex **59** which underwent carbonylation and subsequent elaboration to afford **56** (Scheme 28).

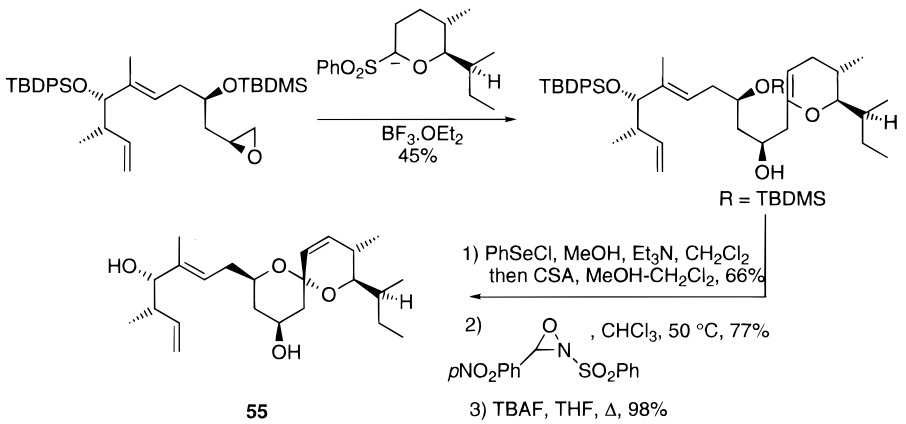
Similarly in our enantioselective total synthesis[38] of the ionophore antibiotic routiennocin (**60**), we have used these methods to prepare a 2-(phenylsulfonyl)-pyran **61** which was transformed through spirocyclization to the natural product (Scheme 29).

III. (π-Allyl)tricarbonyliron Lactam Complexes

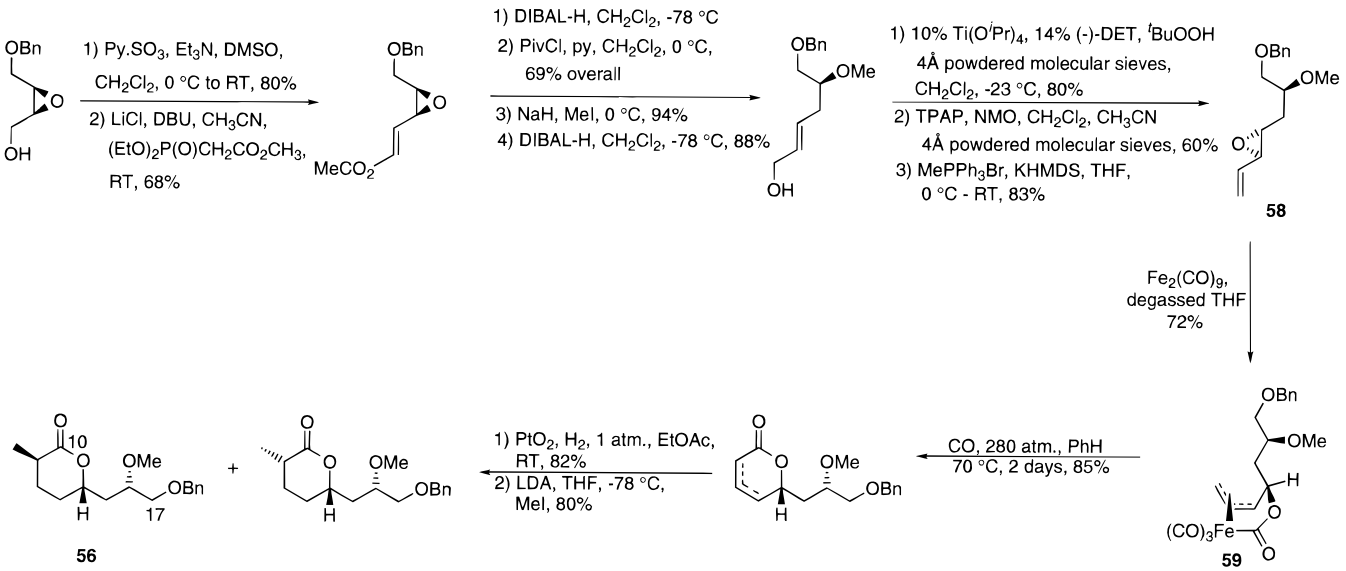
In 1974 Shvo reported the first (π-allyl)tricarbonyliron lactam complexes which were formed by reacting the corresponding lactone complexes such as **3** or **62** with primary amines in the presence of basic or neutral alumina[6] (Scheme 30), which was essential for this reaction to proceed. By using substituted examples, such as **62**, the authors showed that an S_N2'-like process was operating during the formation of the lactam product **63**. In a more detailed study of the mechanism, deuterio-labeled substrates were employed to confirm the nature of the S_N2'-like process.[39]

Shvo also showed that reaction of the oxazine **64** with diiron nonacarbonyl produced an unstable (π-allyl)tricarbonyliron lactam complex **65** which readily

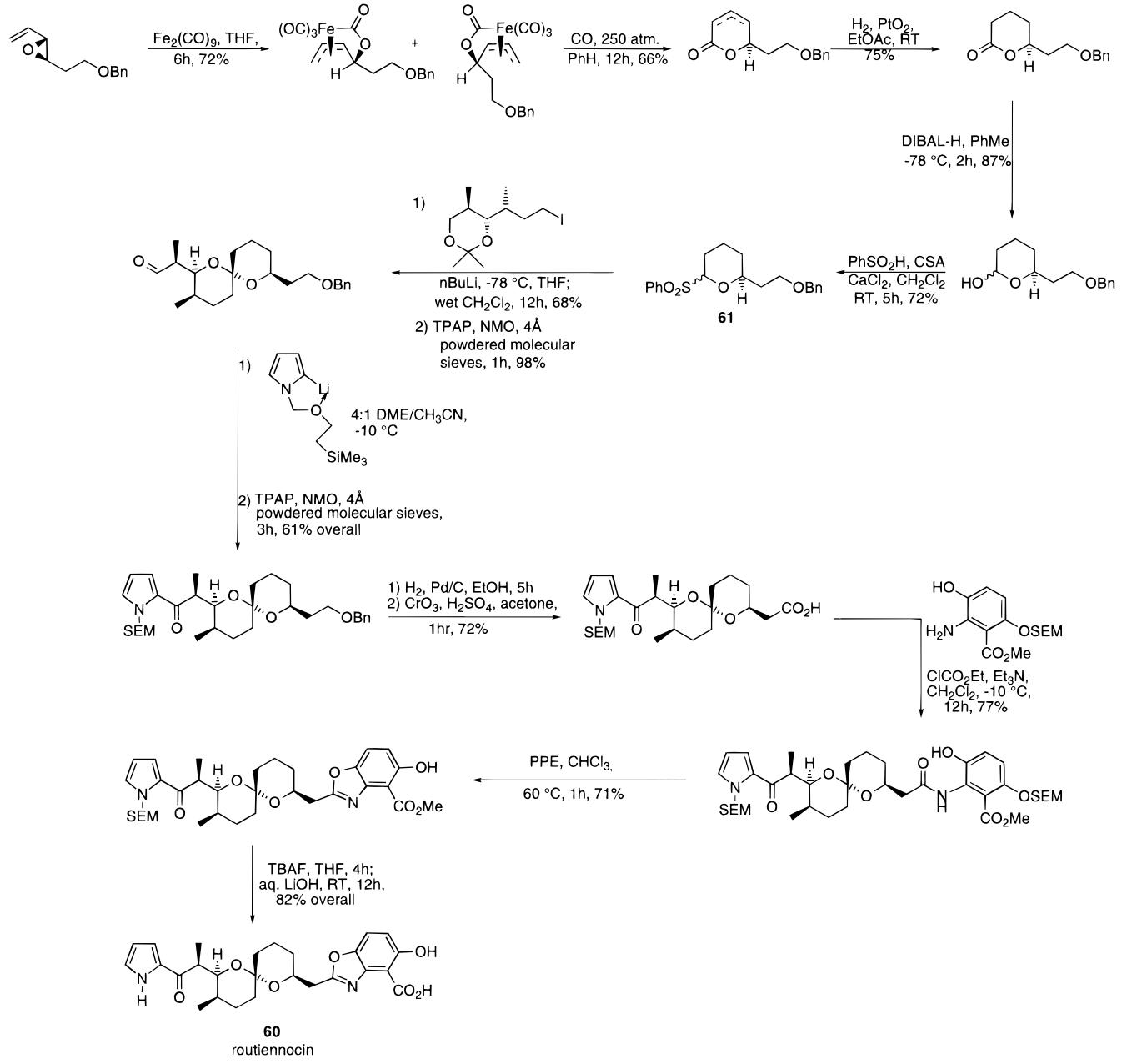
Scheme 27



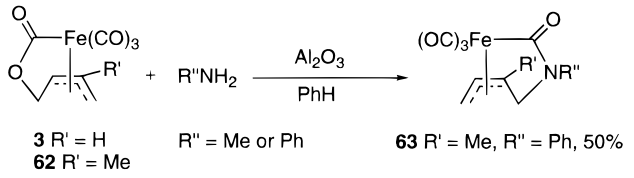
Scheme 28



Scheme 29

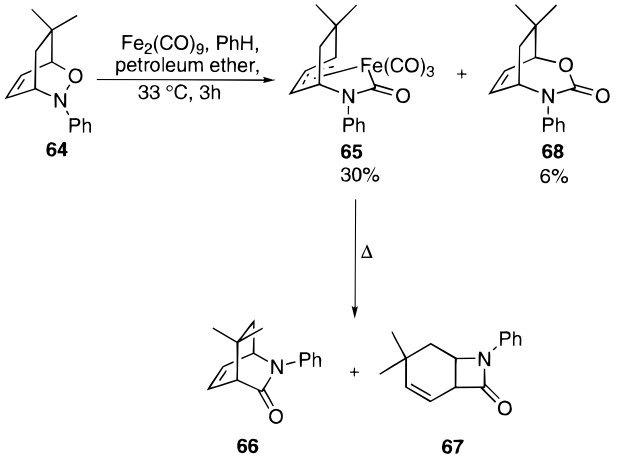


Scheme 30



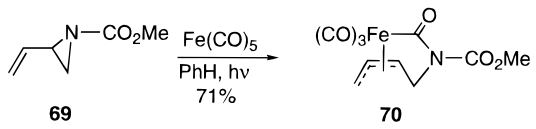
decomposed upon heating to form **66** and **67**. Treatment of the oxazine **64** also gave rise to the cyclic carbamate **68**, arising from insertion of carbon monoxide into the N−O bond, in low yield[40] (Scheme 31).

Scheme 31



An alternative route to lactam complexes was established by Aumann in 1974.[7] He reported the conversion, in good yield, of a vinyl aziridine **69** with iron pentacarbonyl, under irradiation conditions, to the corresponding lactam complex **70** (Scheme 32).

Scheme 32

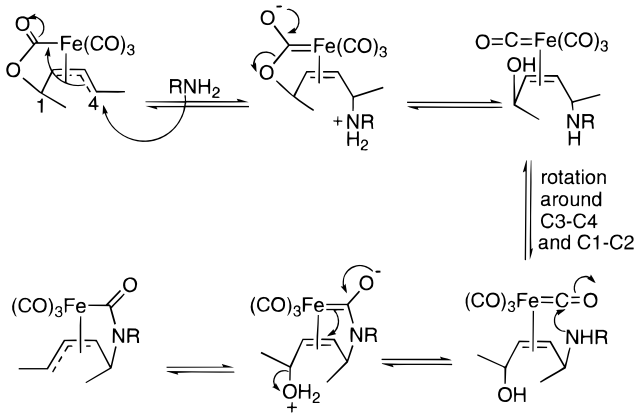


Later Aumann investigated the stereochemical aspects[9] of the reaction of amines with (π-allyl)-tricarbonyliron lactone complexes in the presence of alumina or aluminum(III) chloride. The reactions were shown to proceed rapidly, in excellent yield, with inversion of configuration at C1 and C4 being observed. This provides further evidence for an S_N2'-like mechanistic pathway, with the necessary rotation around C1−C2 and C3−C4 accounting for the observed stereochemical outcome (Scheme 33).

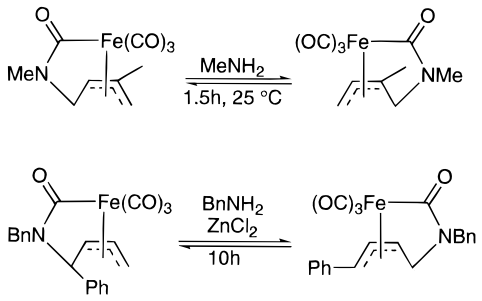
The S_N2'-like products of this reaction are not always exclusively observed, however, as under prolonged reaction conditions transamidation may occur to give scrambled products (Scheme 34).[9,41]

In an effort to find alternative Lewis acids which would effect the conversion of (π-allyl)tricarbonyliron lactone complexes to the corresponding lactams by reaction with primary amines, we found that zinc chloride was effective.[42] The addition of tetramethylethylenediamine was found to have a pronounced effect, further increasing the yield and reducing the reaction time by solubilizing the zinc chloride Lewis

Scheme 33

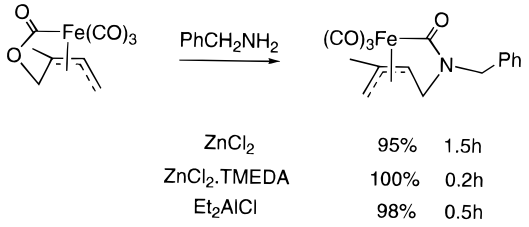


Scheme 34



acid. Other tertiary amines were tried but gave poorer results due to their poorer solubilizing abilities. Alternative Lewis acids, such as diethylaluminum chloride, were also found to be of use in promoting this reaction (Scheme 35). These new,

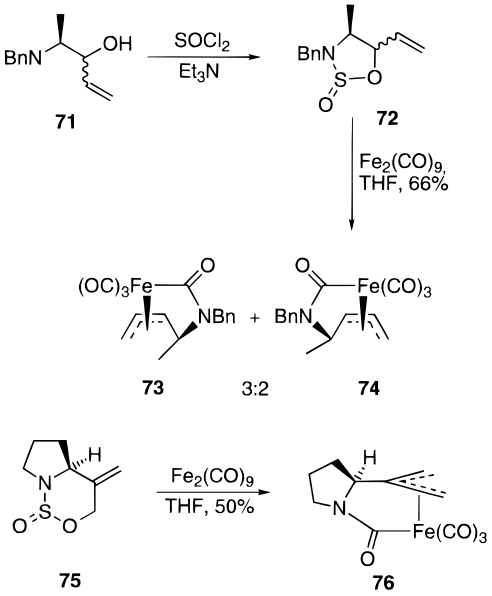
Scheme 35



relatively mild reaction conditions are now our first method of choice for synthesizing tricarbonyliron lactam complexes and have been especially useful when using more sensitive substrates or amines derived from amino acids as precursors for β-lactam synthesis (see later).

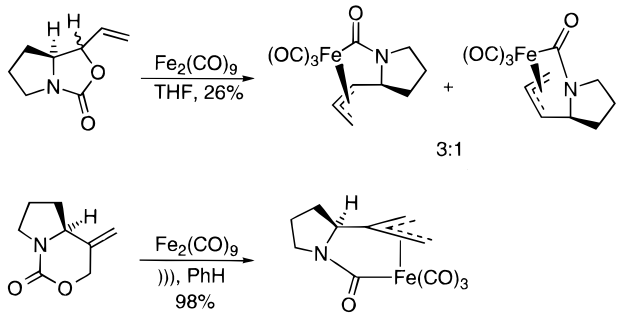
As a more direct route to (π-allyl)tricarbonyliron lactam complexes, which avoids the need to prepare intermediate lactone complexes, we have briefly investigated the use of alkenyl cyclic sulfamidites as precursors.[43] The amino alcohol **71**, for example, which is readily derived from methylalanine, reacts with thionyl chloride to give the sulfamidite **72**. This undergoes reaction with diiron nonacarbonyl in tetrahydrofuran to afford the corresponding *endo* and *exo* complexes, **73** and **74**, in 40% and 26% yield, respectively (Scheme 36). In a similar fashion the cyclic sulfamidite **75**, derived from L-proline, gives complex **76** in good yield.[44] During these reactions there is no detectable racemization of the stereocenter adjacent to the nitrogen substituent.

Scheme 36



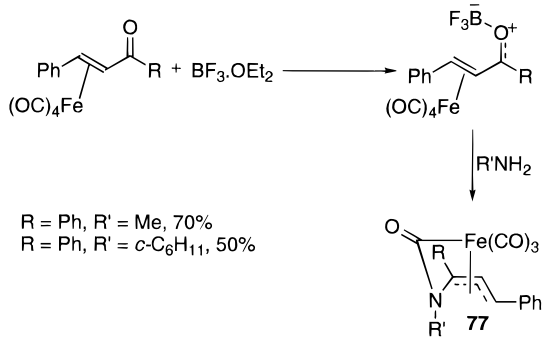
By a related process alkenyl-substituted carbamates also react with diiron nonacarbonyl to afford (π-allyl)tricarbonyliron lactam complexes[43,45] (Scheme 37).

Scheme 37



Finally, a route to (π-allyl)tricarbonyliron lactam complexes **77** has been developed by Rybinskaya which involves the reaction of amines with η^2 tetracarbonyliron chalcone complexes in the presence of boron trifluoride diethyl etherate[46] (Scheme 38). A

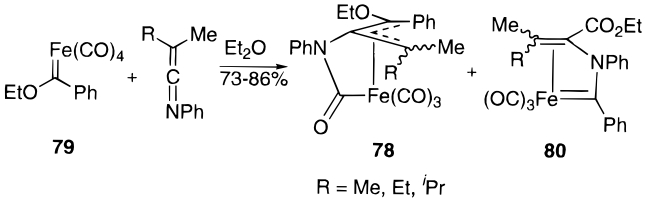
Scheme 38



number of these complexes are now known and have been fully characterized by a variety of methods including X-ray crystallography. Intermediates in the reaction pathway have also been determined. So far, however, none of these (π-allyl)tricarbonyliron lactam complexes have been employed in organic synthesis.

Other related complexes including **78** have been prepared by reacting carbene complexes such as **79** with ketenimines in diethyl ether at 50 °C.[47] A formal [2 + 2] cycloaddition of the ketenimine to form a metallacycle which subsequently undergoes oxidative insertion of carbon monoxide into the Fe−N bond accounts for the formation of this product. A carbene complex **80** is also produced which arises from reversal of the regioselectivity in the initial cycloaddition (Scheme 39).

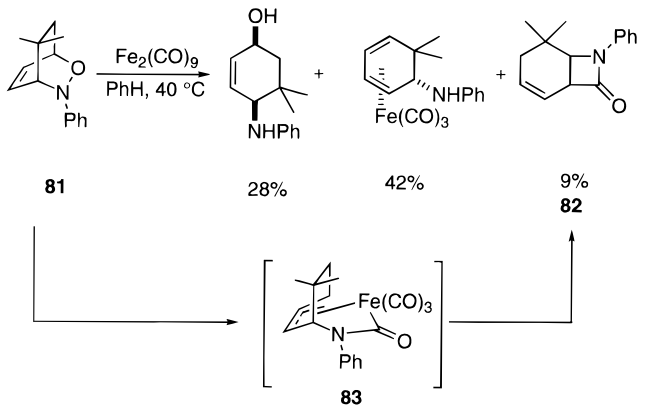
Scheme 39



A. Synthesis of Lactams

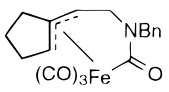
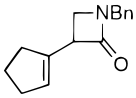
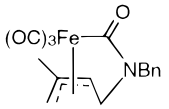
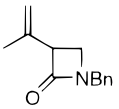
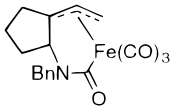
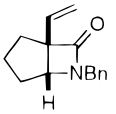
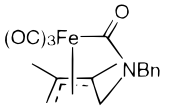
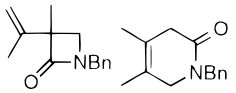
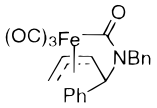
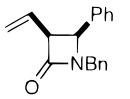
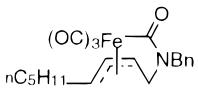
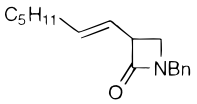
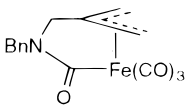
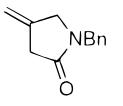
From the early work of Shvo, the formation of lactams as products during the reaction of *N*-phenyl-2-oxo-3-azabicyclo[2.2.2]oct-5-enes **81** with diiron nonacarbonyl at 40 °C in benzene suggested the possible intermediacy of (π-allyl)tricarbonyliron lactam complexes.[40] Generally, however, the yields were too low (i.e. less than 10%) to be preparatively useful. As a typical example of this process, when **81** was reacted with diiron nonacarbonyl, three products were obtained with the β-lactam **82** being formed in only 9% yield. The intermediacy of (π-allyl)tricarbonyliron lactam complex **83** was proposed to account for the formation of the lactam **82** (Scheme 40).

Scheme 40



On the basis of our observations with lactone complexes, which were selectively decomplexed by treatment with ceric ammonium nitrate, we initiated a study with the corresponding lactam derivatives in the hope that these would be converted to β-lactams in preparatively useful yields. This concept was realized: lactam complexes were readily transformed, in good to excellent yield, to the required lactams upon reaction with ceric ammonium nitrate at −30 °C.[42] In Table 2 are illustrated some examples of these selective lactam forming reactions. All the lactam complexes in this study were prepared

Table 2

lactam complex	product(s)	yield (%)
		87
		89
		75
		34,54
		78
		64
		56

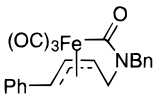
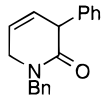
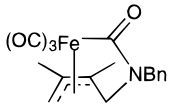
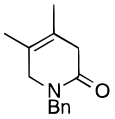
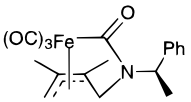
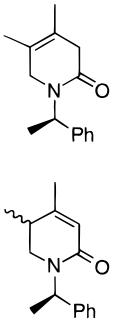
in high yield from the corresponding lactone complexes by treatment with amines in the presence of zinc chloride or diethylaluminum chloride according to our previously described procedure.

In a few isolated examples we have also investigated the exhaustive carbonylation of (π-allyl)tricarbonyliron lactam complexes to afford selectively δ-lactams[23] (Table 3). The generality of this reaction, however, has yet to be explored.

B. Natural Product Synthesis

Owing to the importance of β-lactams as antibiotics we have sought to apply our methods to more challenging, biologically active target molecules. In the first of these syntheses we have prepared a hydroxyethyl-substituted β-lactam which had previously been converted to the potent antibiotic (+)-thienamycin (**84**).[48] The route harnesses the interconversion of lactone complexes to lactams using

Table 3

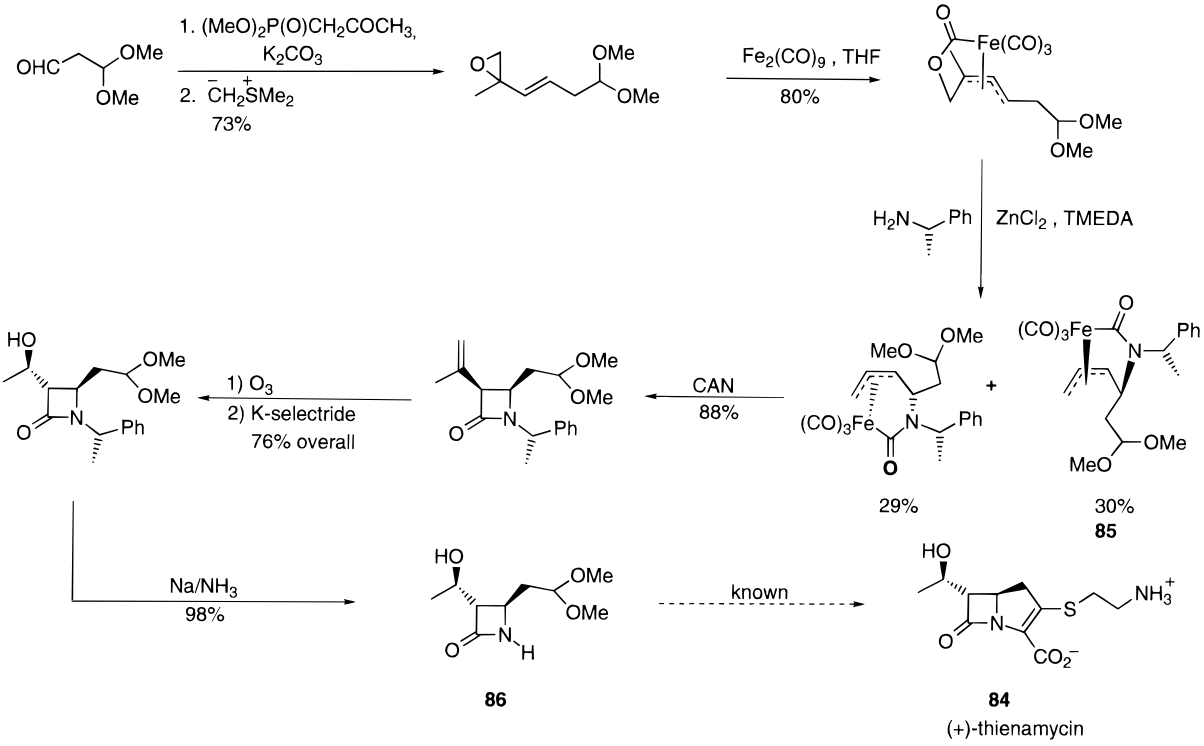
lactam complex	conditions	product(s)	yield (%)
	300 atm. CO 90 °C		55
	300 atm. CO 90 °C		72
	300 atm. CO 90 °C		79
		1:1 mixture	

chiral benzyl amines to facilitate diastereoisomer separation. Moreover the chiral benzyl group also acts as a protecting group for the nitrogen atom during further transformations. The separated, and required, complex **85** is eventually unmasked to the parent β-lactam **86** at the end of the sequence[49] (Scheme 41).

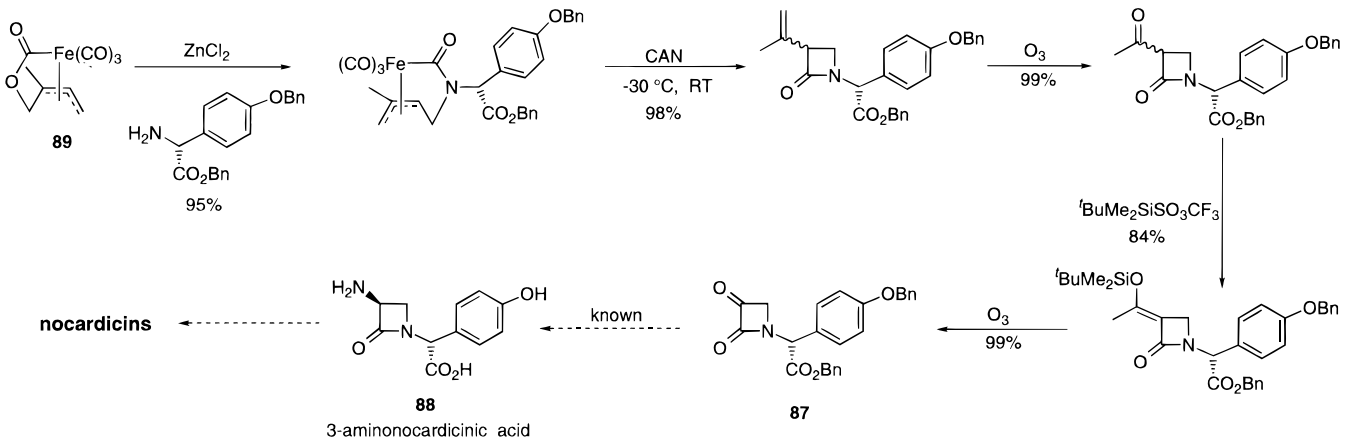
In another application of these methods we have synthesized a 3-oxo azetidinone **87** by a short and highly efficient route from isoprene.[50] This compound had previously been used as a precursor for the synthesis of 3-aminonocardicinic acid (**88**), which was the starting point for the preparation of the nocardicin antibiotics.[51] The pathway to the azetidinone **87**, which is outlined in Scheme 42, begins with the tricarbonyliron lactone complex **89**, derived from isoprene monoepoxide. This was converted to the corresponding lactam using (*S*)-dibenzyl *p*-(oxyphenyl)glycine, in association with zinc chloride catalysis, without any detectable racemization of the amino acid stereogenic center. After conversion to the β-lactam, the propene side chain was oxidatively cleaved to furnish the 3-oxo derivative **87** in excellent yield.

Finally, we have used these methods in the formal syntheses of two pyrrolizidine alkaloids, heliotridane (**90**) and isoretronecanol (**91**).[44] These syntheses rely upon the reaction of the cyclic carbamate **92**, derived from L-proline, with diiron nonacarbonyl to give the lactam complex **93**. This was then smoothly converted to the β-methylene lactam **94**, by either one-electron oxidation executed by ceric ammonium nitrate or exhaustive carbonylation, which forms the pivotal point for the two syntheses (Scheme 43).

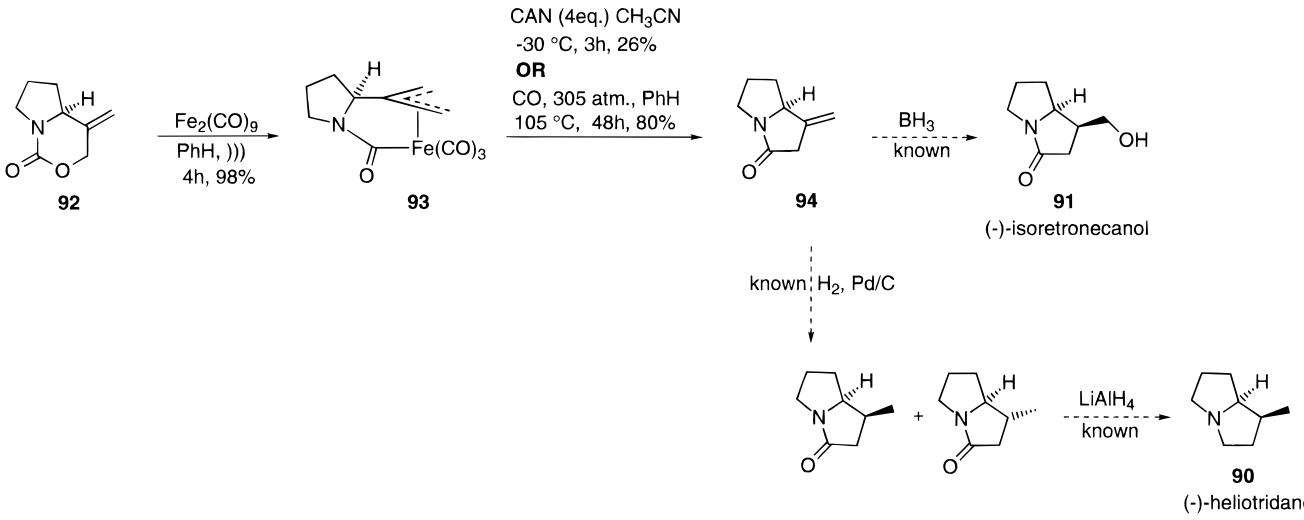
Scheme 41



Scheme 42



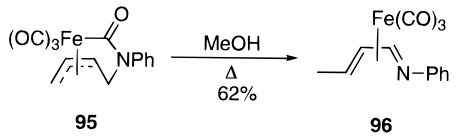
Scheme 43



IV. Thermal Reactions of Lactone and Lactam Complexes

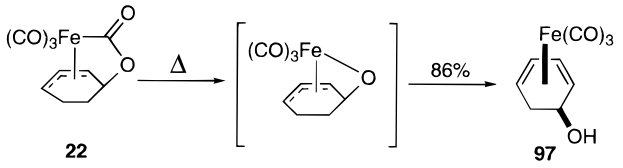
Several thermolytic reactions of these complexes have been reported, some of which lead to potentially useful products. The distribution of products, however, arising from isomerization, decarbonylation, or decarboxylation reactions does not follow any consistent pattern. In this section the reactions are discussed in an approximate chronological order. Shvo has reported the rapid thermal conversion of the lactam complex **95** in boiling methanol to give the imine complex **96**. The mechanism of this process is thought to involve a decarbonylation and a 1,4 intramolecular hydrogen shift[6] (Scheme 44).

Scheme 44



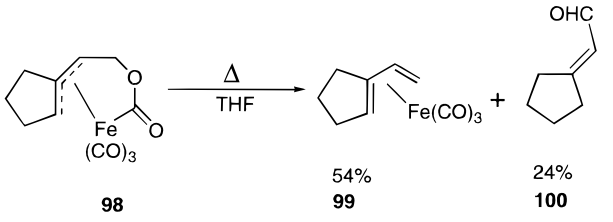
Upon warming the lactone complex **22**, Aumann observed rapid loss of carbon monoxide followed by isomerization to the (η^4-diene)tricarbonyliron hydroxy complex **97**[7] (Scheme 45).

Scheme 45



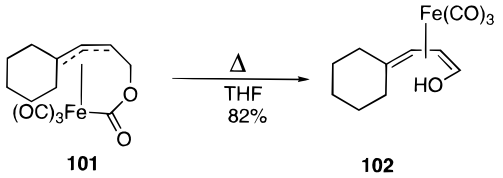
In other more detailed studies we showed that lactone complexes underwent a number of different reaction pathways while heating in tetrahydrofuran or benzene solutions.[52] On boiling, in tetrahydrofuran, for example, the lactone complex **98** gave the (η^4-diene)tricarbonyliron complex **99** along with the enal **100** (Scheme 46).

Scheme 46



In other synthetically relevant experiments, it was found that the complex **101** furnished the enol (η^4-diene)tricarbonyliron complex **102** as a single product in 82% yield upon heating in tetrahydrofuran (Scheme 47). This reaction is interesting as the product

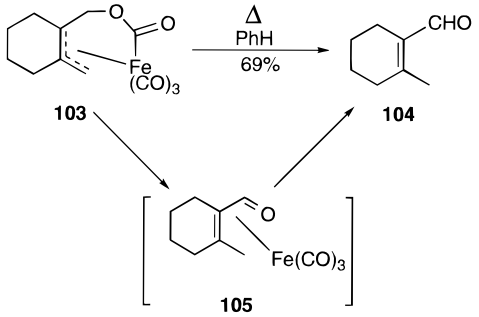
Scheme 47



constitutes an example of a stabilized enol species[53] which could, potentially, be useful for further transformations.

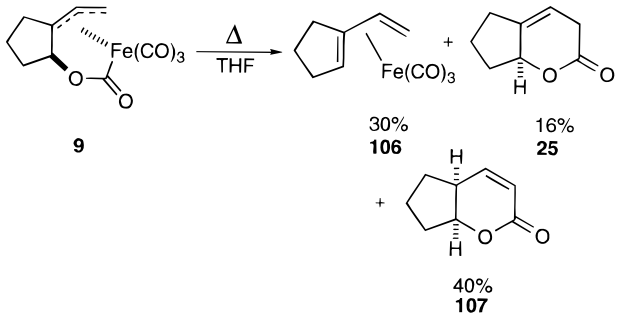
On heating **103** in benzene at 60 °C the enal **104** was produced after oxidative workup with trimethylamine *N*-oxide in 69% yield. The necessity of an oxidative workup suggests the intermediacy of a η^4 tricarbonyliron enal complex **105**, presumably formed by decarbonylation with concomitant hydrogen migration (Scheme 48).

Scheme 48



Other complexes on heating lead to the formation of δ-lactones, such as **9**, which when warmed in tetrahydrofuran for 2.5 h led to a mixture of products **106**, **107**, and **25** (Scheme 49).

Scheme 49



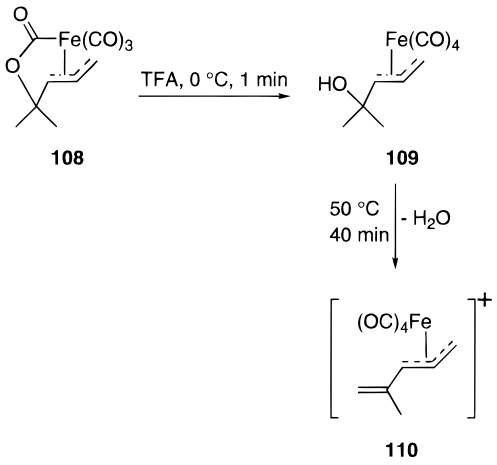
Many other examples of complexes were investigated and mechanisms to account for the various transformations were discussed in detail.[52]

V. Reactions with Acids and Bases

Owing to the lability of many of these complexes, few reactions which lead to characterizable products with acids and bases have been reported. In general, these complexes tend to be fairly stable to mild acids, although with strong acids, such as trifluoroacetic acid (TFA), fragmentation ensues. By ^{1}H NMR spectroscopy it is possible to observe decomposition intermediates that are produced upon exposure of **108** to trifluoroacetic acid at 0 °C.[9] The protonated species thought to be **109**, for example, can be detected after only 1 min. On warming to 50 °C for 40 min dehydration leads to the detectable cation **110** being produced (Scheme 50). It is not possible, however, to isolate any products from these reaction mixtures.

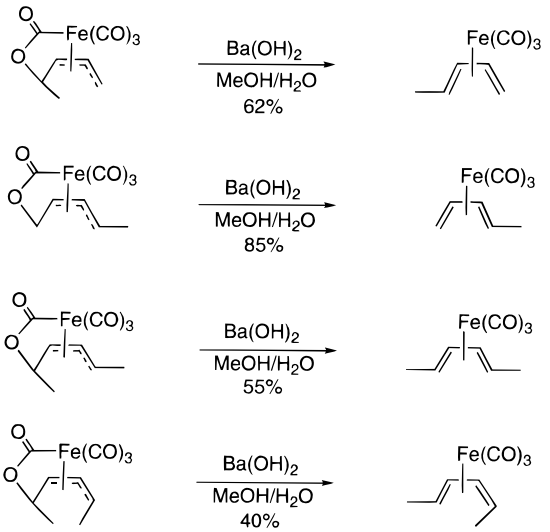
One of the most important and useful reactions of (π-allyl)tricarbonyliron lactone complexes occurs when

Scheme 50



they are treated with barium hydroxide in aqueous methanol. Under these conditions rapid formation of the corresponding (η^4-diene)tricarbonyliron complex is observed[9] (Scheme 51). Barium hydroxide is

Scheme 51

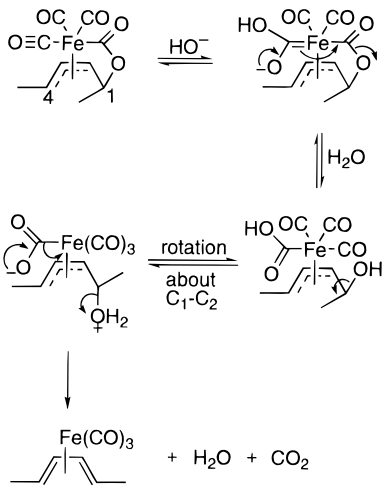


the usual source of hydroxide anions because its low solubility in aqueous methanol ensures only a low concentration of the reactive species in solution at any one time thus the number of side reactions leading to undesirable byproducts is reduced.

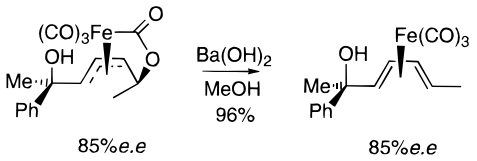
In these highly stereoselective decarboxylations, inversion of configuration of stereochemistry occurs only at C1. This is in accord with the hydroxide nucleophile attacking a terminal carbonyl group and not the allyl system. Subsequent fragmentation of the lactone, rotation around the C1−C2 bond, followed by concerted decarboxylation and dehydration accounts for the observed stereochemical outcome of the reaction[9] (Scheme 52).

We have used this barium hydroxide procedure developed by Aumann to prepare homochiral (*E*,*E*)-(η^4-diene)tricarbonyliron complexes,[3] an example of which is shown in Scheme 53. In accord with the proposed mechanism, no loss of enantiopurity was observed during the reaction process.

Scheme 52



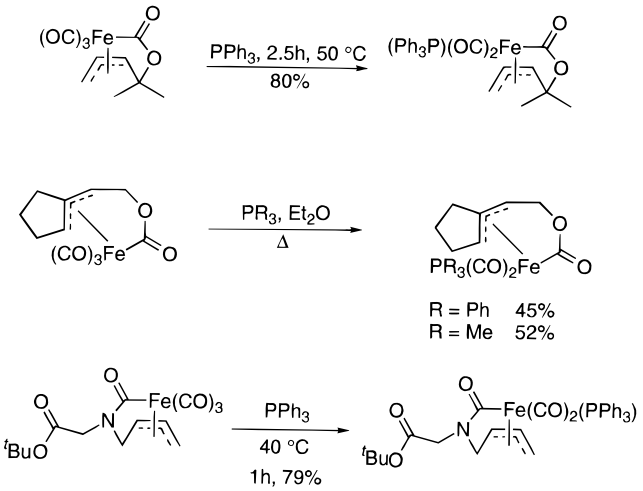
Scheme 53



VI. Ligand Exchange: Reaction with Phosphines

Several groups have reported the exchange of one of the carbonyl ligands in (π-allyl)tricarbonyliron lactone[9,54] and lactam[55] complexes by treatment with phosphines. No evidence, however, has been presented describing which particular carbonyl ligand group is exchanged during this process (Scheme 54).

Scheme 54



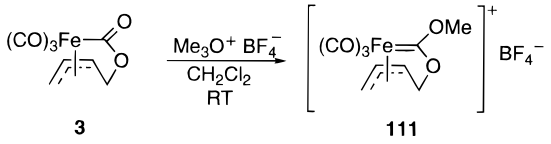
To date, none of these complexes have proved to be useful in synthesis owing to the fact they are noticeably more stable than the corresponding tricarbonyl species.

VII. Carbene Complexes

We first prepared carbene complexes from (π-allyl)-tricarbonyliron lactone complexes in 1986 by standard treatment of **3** with 4.5 equiv of Meerwein's reagent.[56] In this fashion we were able to convert the lactone complex **3** to the carbene complex **111** in

95% yield (Scheme 55). We envisaged that this species might react with a variety of nucleophiles.

Scheme 55

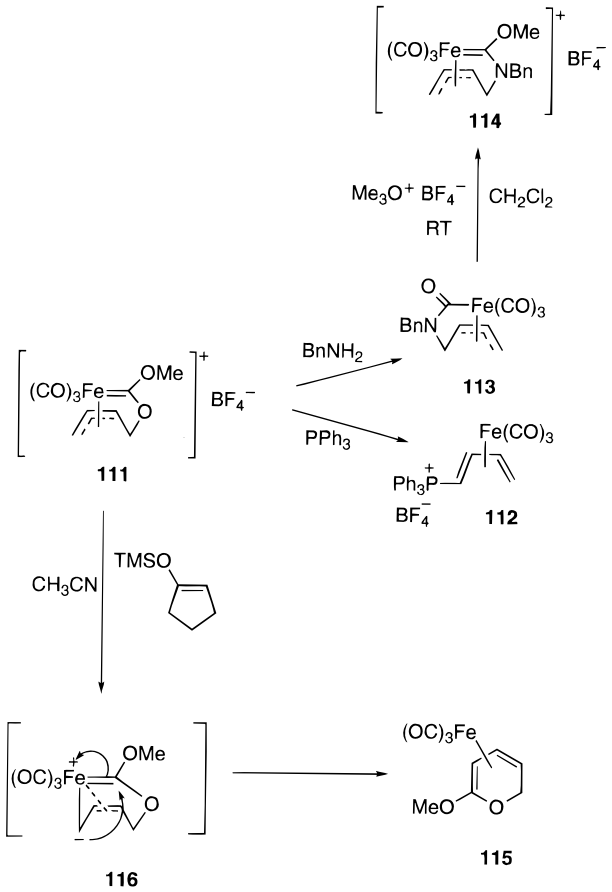


3 111

Disappointingly, however, despite studying a large number of reagents which included phenylmagnesium bromide, methyllithium, hydrogen peroxide, ceric ammonium nitrate, sodium borohydride, diisobutylaluminum hydride, *o*-benzylhydroxylamine, *N*-hydroxysuccinimide, indole, aldehydes, ketones, cyclohexene, methyl acrylate, methyl chloroformate, sodium acetate, acetic anhydride, and sodium hydride no identifiable products were isolated.

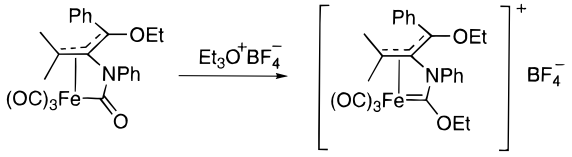
However, Schobert, who worked in our group, has continued to study these systems and has recently produced interesting results.[57] He has demonstrated that the carbene complex **111** reacts with triphenylphosphine to afford a phosphonium salt **112** and with benzylamine to furnish a lactam complex **113**. This species, when treated with Meerwein's reagent, gave the corresponding carbene complex **114**, further extending the previous methodology. The carbene **111** also reacts with silyl enol ethers to afford (η^4-diene)tricarbonyliron pyran derivatives **115** via a curious mechanism involving the presumed intermediate **116** (Scheme 56).

Scheme 56



A further crystalline carbene derivative of a lactam complex has been reported[47] in which the π-allyl derivative **117** reacts with a Meerwein reagent to give **118** (Scheme 57).

Scheme 57



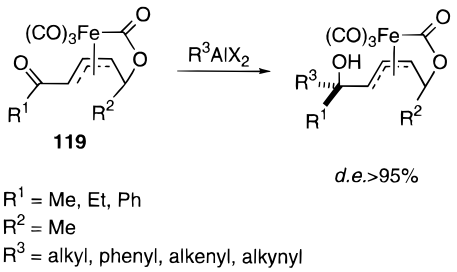
117 118

VIII. Asymmetric Induction Using (π-Allyl)-tricarbonyliron Lactone Complexes

Substituted (π-allyl)tricarbonyliron lactone complexes are inherently chiral owing to the complexation of the iron to either stereoface of the allyl unit. These complexes may also be prepared in enantiopure form by appropriate choice of the starting materials. It is reasonable, therefore, to harness these properties for asymmetric synthesis. It was envisaged that the bulk of the tricarbonyliron unit, in association with the rigidity of the lactone tether, would allow for stereoselective reactions of carbonyl groups in the periphery of the allyl unit.[3]

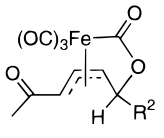
In the main we have concentrated on the addition of organoaluminum reagents to ketones placed adjacent to the allyl unit and on examining the diastereoselectivity in the formed tertiary hydroxy products (Scheme 58). We have found that for a wide

Scheme 58



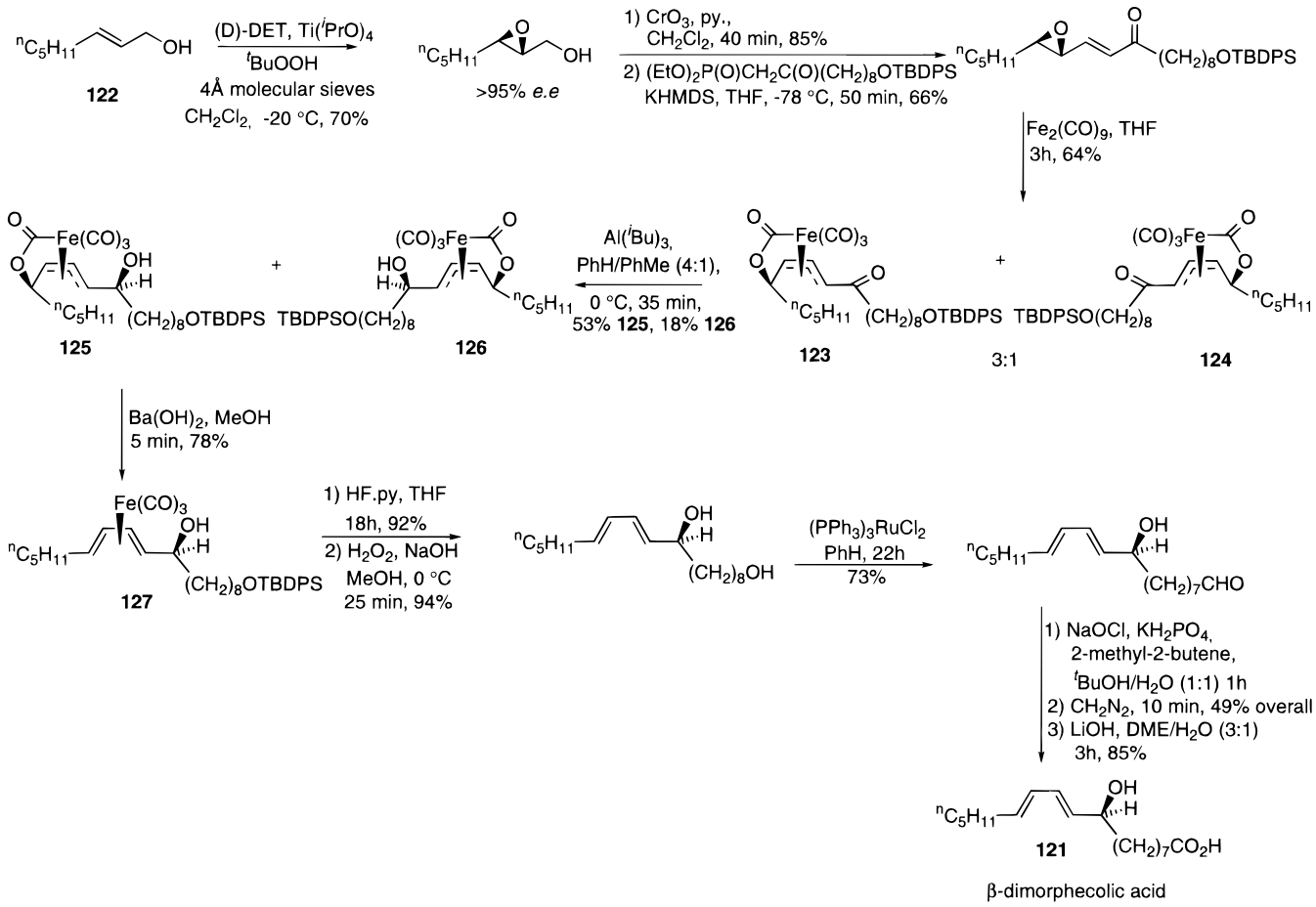
variety of organoaluminum reagents the yields are high and the diastereoisomeric excess of the product is always greater than 95% as shown in Scheme 58. This was an extremely pleasing result and compared very favorably with related methods.[58] Application of the barium hydroxide protocol described earlier occurs smoothly to afford the (η^4-diene)tricarbonyliron complexes without loss of diastereoisomeric purity (Scheme 53).

Although Scheme 58 indicates the results obtained with the *endo*-complexes **119**, similar excellent diastereoselectivity can be obtained by addition to the corresponding *exo*-compounds **120**.



120

Scheme 59



The relative stereochemical outcome of all these reactions was established through X-ray crystallographic structural determination and extensive NMR studies. In addition, comparison of derivatives with authentic samples of known configuration[59] supported our stereochemical assignments.

A. Synthesis of β-Dimorphecolic Acid

Having established that high facial selectivity could be achieved in the addition of organoaluminum reagents to carbonyl groups in (π-allyl)tricarbonyliron lactone complexes, we set about using these methods in the preparation of a natural product. β-Dimorphecolic acid (**121**), which was first isolated from the seed oil of *Dimorphotheca aurantiaca*,[60] belongs to a family of hydroxy fatty acids which possess important biological activity.[61] Previously no enantioselective synthesis of **121** had been reported, although one synthesis of racemic material has been accomplished by Alexakis.[62]

In the previous section we reported the very high stereoselectivity that could be realized in the addition reactions of organoaluminum reagents to side chain carbonyl groups in (π-allyl)tricarbonyliron lactone complexes. We anticipated that equally high facial selectivity could be obtained in reduction of the side chain carbonyl group. This is in fact the case and forms the basis of the control in the synthesis of our target[63] (Scheme 59). The initial stereochemistry is set in place by use of the catalytic asymmetric Sharpless epoxidation[39] of the allylic alcohol **122**. After elaboration to a suitable alkenyl epoxide, this was converted to the diastereoisomeric (π-allyl)-tricarbonyliron lactone complexes **123** and **124**. These were not separated at this stage but were reduced in a highly diastereoselective fashion with triisobutylaluminum to the corresponding alcohols **125** and **126**. Analysis of these alcohols by ^{1}H NMR and HPLC revealed the presence of only these diastereoisomers. Furthermore, formation of the corresponding Mosher esters[64] revealed both of these alcohols to have enantiomeric excesses greater than 95%. After separation of the major, and required, isomer **125**, this was transformed to the (η^4-diene)tricarbonyliron complex **127** with barium hydroxide and eventually to β-dimorphecolic acid (**121**).

This synthesis, which is relatively short and highly stereoselective, demonstrates the utility of carbonyl-substituted (π-allyl)tricarbonyliron lactone complexes for natural product synthesis. The tricarbonyliron tether exerts control over two distinct elements of stereochemistry, namely a 1,5-asymmetric induction to form the required stereogenic center followed by a stereoselective decarboxylation reaction to control the (*E*,*E*)-diene geometry.

IX. Concluding Remarks

While the chemistry reported above provides interesting and new opportunities for organic synthesis using (π-allyl)tricarbonyliron complexes, one can expect further chemistry to emerge which will explore other aspects of these unusual templating species.

Many of the reactions are conceptually fairly general and as such, it might be possible to develop catalytic systems with other metals to avoid the use of the stoichiometric processes.

Nevertheless (π-allyl)tricarbonyliron lactone complexes do provide an attractive and useful scaffolding for further synthetic transformation leading to natural products, many of which have important biological activity.

X. Acknowledgments

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XI. References

(1) Zeise, W. C. *Ann. Phys.* **1827**, *9*, 932.
(2) Ley, S. V. *Philos. Trans. R. Soc. A* **1988**, *326*, 633.
(3) Ley, S. V.; Meek, G.; Metten, K. H.; Piqué, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1931.
(4) Murdoch, H. D. *Helv. Chim. Acta* **1964**, *47*, 936.
(5) Heck, R. F.; Boss, C. R. *J. Am. Chem. Soc.* **1964**, *86*, 2580.
(6) Becker, Y.; Eisenstadt, A.; Shvo, Y. *Tetrahedron* **1974**, *30*, 839.
(7) Aumann, R.; Fröhlich, K.; Ring, H. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 275.
(8) Chen, K. N.; Moriarty, R. M.; DeBoer, B. G.; Churchill, M. R. *J. Am. Chem. Soc.* **1975**, *97*, 5602.
(9) Aumann, R.; Ring, H.; Krüger, C.; Goddard, R. *Chem. Ber.* **1979**, *112*, 3644.
(10) Pearson, A. J. *Metallo-Organic Chemistry*; Wiley: Chichester, 1985.
(11) Annis, G. D.; Ley, S. V.; Sivarakmakrishnan, R. *J. Organomet. Chem.* **1979**, *182*, C11−C14.
(12) Cotton, F. A.; Troup, J. M. *J. Am. Chem. Soc.* **1974**, *96*, 3438. Cotton, F. A.; Troup, J. M. *J. Am. Chem. Soc.* **1974**, *96*, 4422.
(13) (a) Horton, A. M.; Hollinshead, D. M.; Ley, S. V. *Tetrahedron* **1984**, *40*, 1737. (b) Ley, S. V.; Low, C. M. R. Reactivity and Structure Concepts in Organic Chemistry. *Ultrasound in Synthesis*; Springer-Verlag: Berlin, Heidelberg, 1989; Vol. 27.
(14) Bates, R. W.; Díez-Martin, D.; Kerr, W. J.; Knight, J. G.; Ley, S. V.; Sakellaridis, A. *Tetrahedron* **1990**, *46*, 4063.
(15) Aumann, R.; Melchers, H. D.; Weidenhaupt, H. J. *Chem. Ber.* **1987**, *120*, 17.
(16) Caruso, M.; Knight, J. G.; Ley, S. V. *Synlett* **1990**, 224.
(17) For use of cyclic sulfates as epoxide equivalents see: (a) Hoye, T. R.; Crawford, K. B. *J. Org. Chem.* **1994**, *59*, 520. (b) Lohray, B. B. *Synthesis* **1992**, 2771.
(18) (a) Sharpless, K. B.; Kim, B. M. *Tetrahedron Lett.* **1989**, *30*, 655. (b) Sharpless, K. B.; Gao, Y.; Lohray, B. B. *Tetrahedron Lett.* **1989**, *30*, 2623.
(19) Annis, G. D.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1977**, 581.
(20) Annis, G. D.; Ley, S. V.; Sivaramakrishnan, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 270.
(21) Elzinga, J.; Hogeveen, H. *J. Org. Chem.* **1978**, *43*, 745.
(22) Bates, R. W. Ph.D. Thesis, University of London, 1989.
(23) Horton, A. M. Ph.D. Thesis, University of London, 1984.
(24) (a) Weibel, E. K.; Hadvary, P.; Hochuli, E.; Kupfer, H.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081. (b) Umezawa, H.; Aoyagi, T.; Hazato, K.; Uotani, K.; Kojima, F.; Hamada, M.; Takendi, T. *J. Antibiot.* **1978**, *31*, 639. (c) Umezawa, H.; Aoyagi, T.; Uotani, K.; Hamada, M.; Hamada, T.; Takeuchi, T.; Takahasi, T. *J. Antibiot.* **1980**, *33*, 1594. (d) Aldridge, D. C.; Giles, D.; Turner, W. B. *J. Chem. Soc., Chem. Commun.* **1970**, 639. (e) Greenspan, M. D.; Yodkovitz, J. B.; Chen, J. S.; Alberts, A. W.; Martin, I.; Mochales, S.; Monaghan, R. L.; Chabala, J. C.; Schwartz, J. C.; Patchett, A. A. *J. Chem. Soc., Chem. Commun.* **1987**, *40*, 1356.
(25) Kitihara, M.; Asano, M.; Naganawa, H.; Maeda, K.; Hamada, M.; Aoyagi, T.; Umezawa, H.; Iitaka, Y.; Nakamura, H. *J. Antibiot.* **1987**, *40*, 1647.
(26) Bates, R. W.; Fernández-Moro, R.; Ley, S. V. *Tetrahedron* **1991**, *47*, 9929.
(27) Horton, A. M.; Ley, S. V. *J. Organomet. Chem.* **1985**, *285*, C17.
(28) Starr, T. J.; Deig, E. F.; Church, K. K.; Allen, M. B. *Tex. Rep. Biol. Med.* **1962**, *20*, 271.
(29) (a) Sakito, Y.; Tanaga, S.; Asami, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 1223. (b) Babler, J. H.; Invergo, B. J.; Sarussi, S. J. *J. Org. Chem.* **1980**, *45*, 4241. (c) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1981**, *46*, 2439. (d) Matsuo, K.; Kinuta, T.; Tanaka, K. *Chem. Pharm. Bull.* **1981**, *29*, 3070. (e) Torii, S.; Inokuchi, T.; Yoritaka, K. *J. Org. Chem.* **1981**, *46*, 5030. (f) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, 576.
(30) Ley, S. V.; Armstrong, A.; Díez-Martín, D.; Ford, M. J.; Grice, P.; Knight, J. G.; Kolb, H. C.; Madin, A.; Marby, C. A.; Mukherjee, S.; Shaw, A. N.; Slawin, A. M. Z.; Vile, S.; White, A. D.; Williams, D. J.; Woods, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 667.
(31) (a) Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87. (b) Fisher, M. H.; Mrozik, H. *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, 1985.
(32) Ford, M. J.; Knight, J. G.; Ley, S. V.; Vile, S. *Synlett* **1990**, 331.
(33) Díez-Martín, D.; Grice, P.; Kolb, H. C.; Ley, S. V.; Madin, A. *Synlett* **1990**, 326.
(34) Ley, S. V.; Lygo, B.; Sternfeld, F.; Wonnacott, A. *Tetrahedron* **1986**, *42*, 4333.
(35) Ley, S. V.; Norman, J.; Pinel, C. *Tetrahedron Lett.* **1994**, *35*, 2095.
(36) (a) Anderson, J. C.; Ley, S. V.; Marsden, S. P. *Tetrahedron Lett.* **1994**, *35*, 2087. (b) Kouklovsky, C.; Ley, S. V.; Marsden, S. P. *Tetrahedron Lett.* **1994**, *35*, 2091.
(37) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(38) Díez-Martín, D.; Kotecha, N. R.; Ley, S. V.; Mantegani, S.; Carlos Menéndez, J.; Organ, H. M.; White, A. D.; Banks, B. J. *Tetrahedron* **1992**, *48*, 7899.
(39) Becker, Y.; Eisenstadt, A.; Shvo, Y. *Tetrahedron* **1976**, *32*, 2123.
(40) Becker, Y.; Eisenstadt, A.; Shvo, Y. *Tetrahedron* **1978**, *34*, 799.
(41) Hollinshead, D. M. Ph.D. Thesis, University of London, 1984.
(42) Annis, G. D.; Hebblethwaite, E. M.; Hodgson, S. T.; Hollinshead, D. M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2851.
(43) Cappi, M. W. Ph.D. Thesis, University of London, 1994.
(44) Knight, J. G.; Ley, S. V. *Tetrahedron Lett.* **1991**, *32*, 7119.
(45) Knight, J. G.; Metten, K. H.; Ley, S. V. Unpublished observations.
(46) Nesmayanov, A. N.; Rybinskaya, R.; Rybin, L. V.; Gubenko, N. T.; Bokii, N. G.; Batsanov, A. S.; Struchkov, Y. T. *J. Organomet. Chem.* **1978**, *149*, 177.
(47) Aumann, R.; Trentmann, B.; Dartmann, M.; Krebs, B. *Chem. Ber.* **1991**, *124*, 1795.
(48) Kametani, T.; Huang, S. P.; Nagahara, T.; Yokohama, S.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 964.
(49) Hodgson, S. T.; Hollinshead, D. M.; Ley, S. V. *Tetrahedron* **1985**, *41*, 5871.
(50) Hodgson, S. T.; Hollinshead, D. M.; Ley, S. V.; Low, C. M. R.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2375.
(51) (a) Kamiya, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron* **1979**, *35*, 223. (b) Koppel, G. A.; McShane, L.; Jose, F.; Cooper, R. D. G. *J. Am. Chem. Soc.* **1978**, *100*, 3933. (c) Wasserman, H. H.; Hlasta, D. L. *J. Am. Chem. Soc.* **1978**, *100*, 6780. (d) Chiba, K.; Mori, M.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1980**, 770. (e) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 1557. (f) Hatanaka, M.; Noguchi, N.; Ishimaru, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1234.
(52) (a) DePuy, C. H.; Greene, R. N.; Schroer, T. E. *J. Chem. Soc., Chem. Commun.* **1968**, 1225. (b) DePuy, C. H.; Jones, T.; Parlon, R. L. *J. Am. Chem. Soc.* **1974**, *96*, 5602.
(53) Annis, G. D.; Ley, S. V.; Self, C. R.; Sivaramakrishnan, R.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1355.
(54) Self, C. R. Ph.D. Thesis, University of London, 1980.
(55) Ley, S. V.; Schobert, R. Unpublished observation.
(56) Low, C. M. R. Ph.D. Thesis, University of London, 1986.
(57) Förtsch, W.; Hampel, F.; Schobert, R. *Chem. Ber.* **1994**, *127*, 711.
(58) For related stereoselective reactions of substituted (η^4-diene)-tricarbonyliron complexes see: Grée, R.; Lellouche, J. P. *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; Jai Press: Greenwich, 1995; Vol. 4, pp 129−273.
(59) Franck-Neumann, M.; Chemla, P.; Martina, D. *Synlett* **1990**, 641.
(60) Smith, C. R., Jr.; Wilson, T. L.; Melvin, E. H.; Wolff, I. A. *J. Am. Chem. Soc.* **1962**, *82*, 1417.
(61) Duffault, J. M.; Einhorn, J.; Alexakis, A. *Tetrahedron Lett.* **1995**, *36*, 2765 and references therein.
(62) Duffault, J. M.; Einhorn, J.; Alexakis, A. *Tetrahedron Lett.* **1991**, *32*, 3701.
(63) Ley, S. V.; Meek, G. *J. Chem. Soc., Chem. Commun.* **1995**, in press.
(64) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

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