PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Approaches to Natural-Product Synthesis with Organometallic Systems Based on Iron, Molybdenum and Manganese [and Discussion]

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Approaches to natural-product synthesis with organometallic systems based on iron, molybdenum and manganese

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New methods for the construction of quaternary carbon centres, with organoiron and organomolybdenum chemistry, are presented. Regiocontrolled addition of tin enolates to substituted cyclohexadienyliron tricarbonyl complexes leads to a new approach to trichothecene synthesis, illustrated by a short total synthesis of (±)-trichodiene. A new coupling reaction of alkenes and diene–$Fe(CO)_3$ units is described, the outcome of which is equivalent to a [6+2] ene reaction. Some applications of arene–manganese tricarbonyl complexes to the preparation of substituted diaryl ethers are discussed, in the context of synthetic approaches to the glycopeptide antibiotics ristocetin A and vancomycin. Finally, stereocontrolled nucleophilic addition to cycloheptadienyliron complexes is illustrated and applied to a synthesis of the Prelog–Djerassi lactone.

Introduction

This paper is intended to give a brief survey of some of the work being carried out in our laboratory, which aims to develop new methods for stereo- and regiocontrolled carbon–carbon bond formation by using a variety of organometallic π-complexes, and to exploit these methods in the synthesis of contemporary natural product target molecules. The current discussion is divided roughly into three parts: (1) methods for the formation of quaternary carbon centres and their application in trichothecene synthesis; (2) use of arene–manganese tricarbonyl complexes for the construction of subunits found in the glycopeptide antibiotics vancomycin and ristocetin A; and (3) use of a metal moiety as a template for controlling stereochemistry of carbon–carbon bond formation.

Formation of quaternary carbon centres

It is now well established that cyclohexadienyl iron tricarbonyl complexes of general structure **1** undergo addition of a variety of carbon nucleophiles at the substituted (R–) terminus to generate cyclohexadiene complexes of type **2**, because of the directing effect of the methoxy substituent (Pearson 1982). A specific example of this chemistry is shown in figure 1, which also illustrates the facility with which the required dienyl complexes are prepared (Pearson 1977).

For a number of years we have been studying the application of such reactions as key steps in the synthesis of compounds related to the trichothecenes, a family of naturally occurring sesquiterpenes (Tamm 1974; Bamburg & Strong 1971; Doyle & Bradner 1980; McDougal & Schmuff 1985), some examples of which are shown in figure 2. Previous studies showed that complex **1** (R = Me) reacts with the enolate anion **3** to give the product **4** by exclusive attack at the methyl-substituted dienyl terminus of **1** (R = Me) (Pearson & Raithby 1980). An

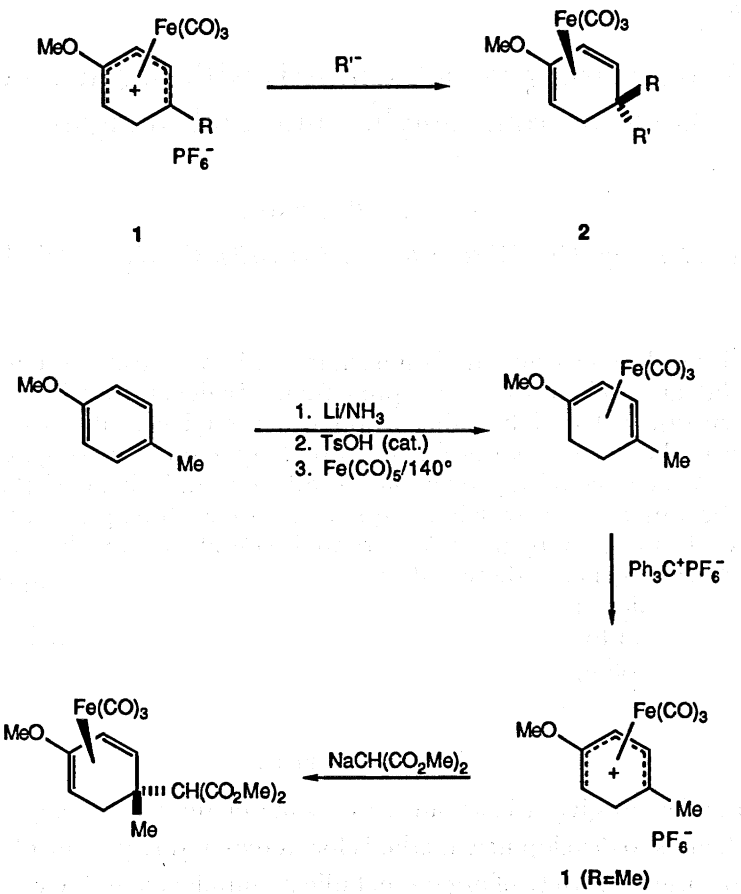


FIGURE 1. Illustration of regiocontrolled carbon–carbon bond formation with dienyliron complexes.

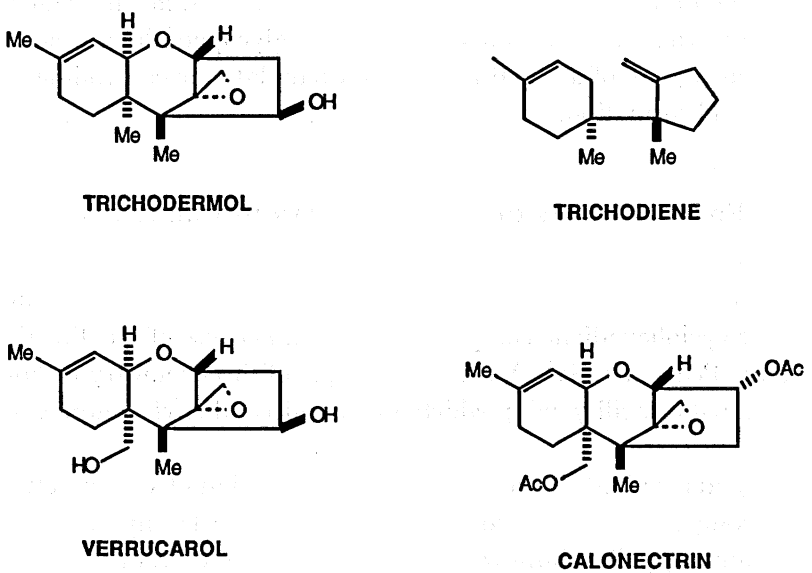


FIGURE 2. Examples of trichothecene natural products.

equimolar mixture of diastereomers is produced and these are readily separated by fractional crystalization. One of the diastereomers (**4a**) has relative stereochemistry at the contiguous quaternary centres appropriate for trichothecene synthesis, and the five-membered ring has been functionalized to produce the analogue compounds **5** (Pearson & Ong 1981) and **6** (Pearson & Chen 1986) (figure 3).

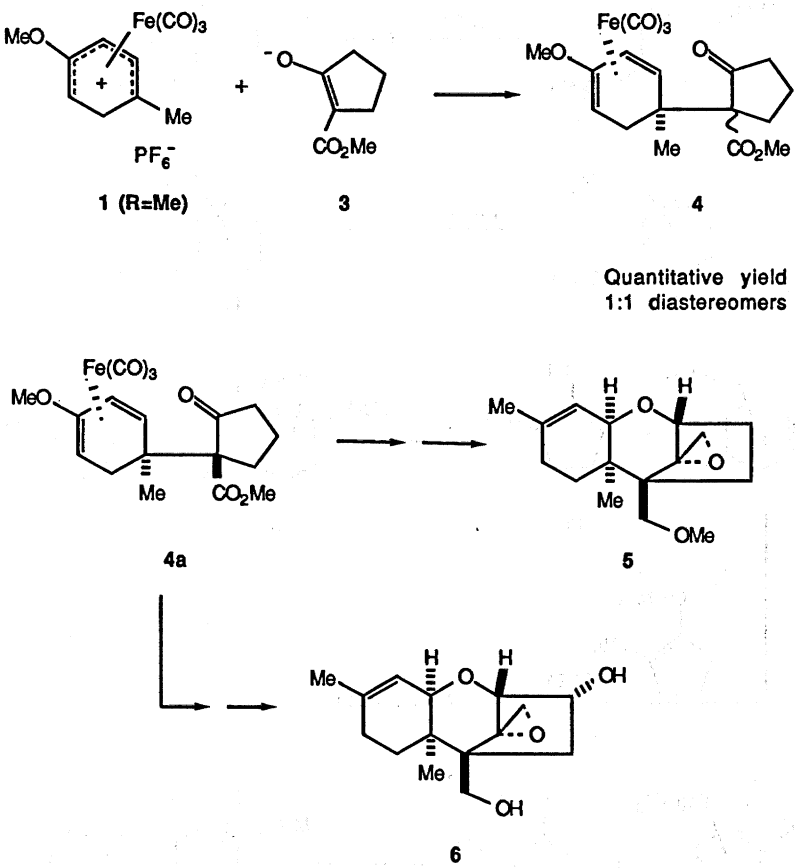
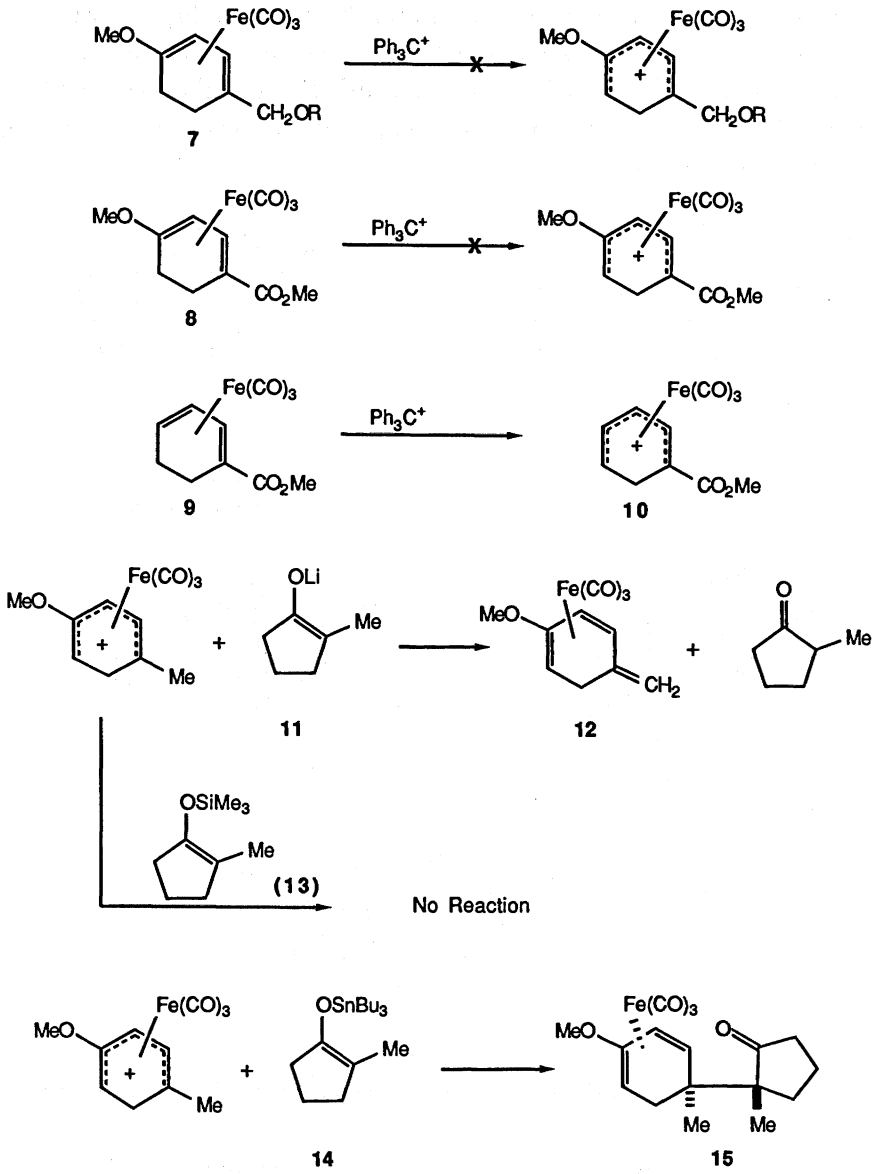


FIGURE 3. Examples of trichothecene analogue synthesis with dienyliron complexes.

However, during these early studies, a number of shortcomings of this approach became apparent, and so a new challenge arose, i.e. to solve such problems by developing new chemistry of these organometallic complexes. These shortcomings may be listed as follows. (1) Conversion of **1** (R = Me) to **4** always gives an equimolar mixture of diastereomers, leading to a loss of at least 50% of material that is not used. (2) To synthesize natural products, such as trichodiene, the ester group of **4** must be reduced to methyl, which is laborious and difficult to realize in practice. (3) The hydride abstraction reaction, in our hands, has so far been unsuccessful on complexes **7** and **8**; this would lead to precursors for verrucarol or calonectrin synthesis (compare this with the successful conversion of **9** to **10** (Birch & Williamson 1973)). Added to these complications is the fact that reaction of **1** (R = Me) with 'hard' enolates such as **11** leads to deprotonation products such as **12**. Although simple dienyliron complexes can be alkylated with silyl enol ethers (Birch *et al.* 1980) this does not provide methodology applicable to trichothecene synthesis, because in our hands reaction between **1** (R = Me) and **13** is unsuccessful.



On the other hand, complex **1** (R = Me) reacts with the tin enolate **14** to give **15** in yields of 90–95% and, fortuitously, this reaction proceeds with marked diastereoselectivity (*ca.* 5:1) to give the isomer shown. This complex was converted in four synthetic operations to racemic trichodiene as shown in figure 4, the most troublesome step being the final 1,4-reduction of diene intermediate, where minor amounts of products from 1,2-reduction are obtained. These are readily separated by chromatography on silver nitrate impregnated silica gel to yield pure trichodiene (Pearson & O'Brien 1987). We are currently investigating the application of this strategy to the synthesis of trichodermol, and in this respect we may note that the dimethylphenylsilyl-substituted enolstannane **16** reacts cleanly with **1** (R = Me) to give **17** in good yield as the major stereoisomeric product. Fleming *et al.* (1984, 1985, 1986, 1987) have developed methods for the conversion of these types of alkylsilane to alcohols, and we anticipate that **17** can be used as a trichodermol precursor. The use of tin enolates in this way offers a

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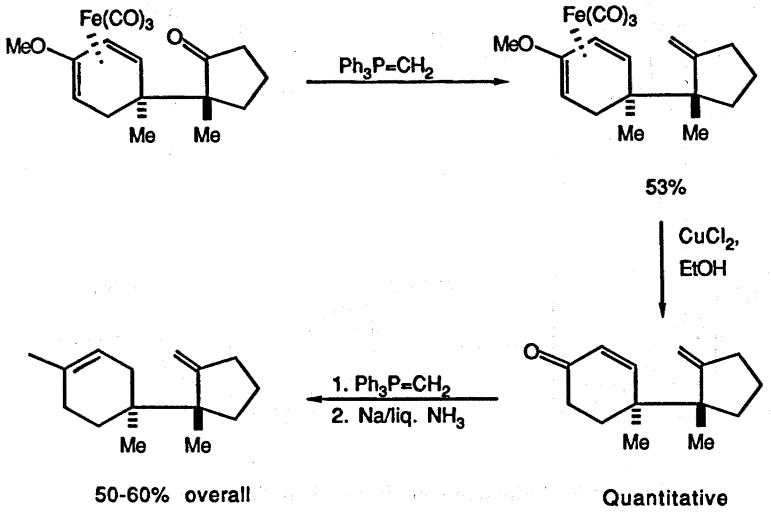
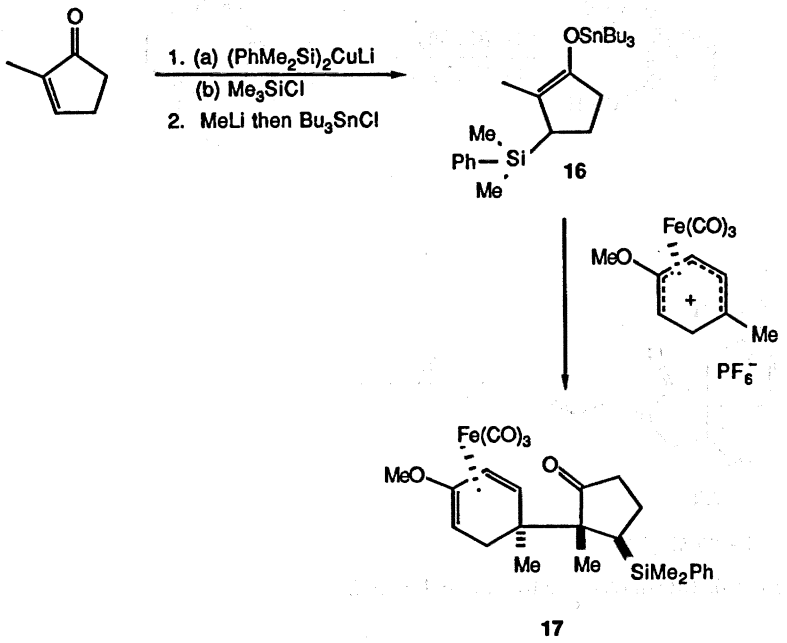


FIGURE 4. Total synthesis of (±)-trichodiene.



solution to the problem of using 'hard' enolates, and obviates the need for stabilized enolates derived from 1,3-dicarbonyl compounds. This strategy is especially promising in view of the fact that complex **1** (R = Me) has been prepared in optically active form (Birch *et al.* 1984).

Ideally, to approach the synthesis of compounds such as verrucarol we should like to be able to alkylate complexes such as **10** at the substituted terminus. Unfortunately, addition of nucleophiles to **10** occurs regiospecifically to give complexes of structure **18**. However, treatment of **10** with zinc dust leads to dimerization to give **20** as the major product in good yield (figure 5), presumably via the free radical intermediate **19** (Pearson *et al.* 1987*a*). We reasoned that such a free radical might undergo reaction with a pendant olefinic group, and so complex **21** was prepared as shown in figure 6. Treatment of this with powdered zinc does

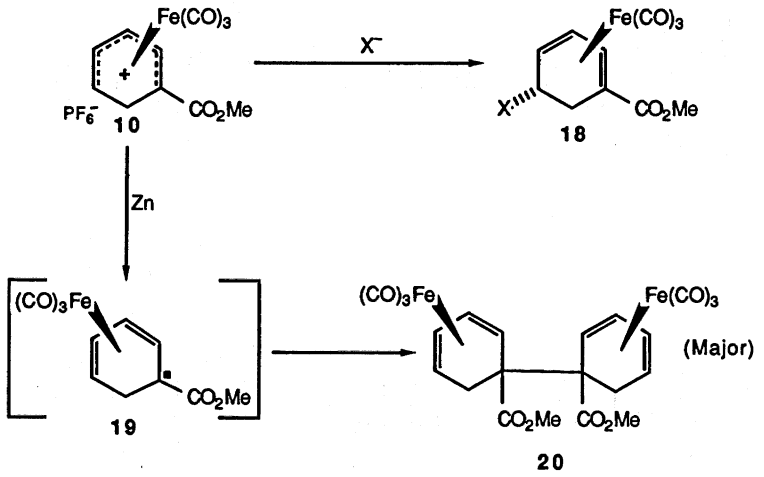


FIGURE 5. Reductive coupling of dienyliron complexes.

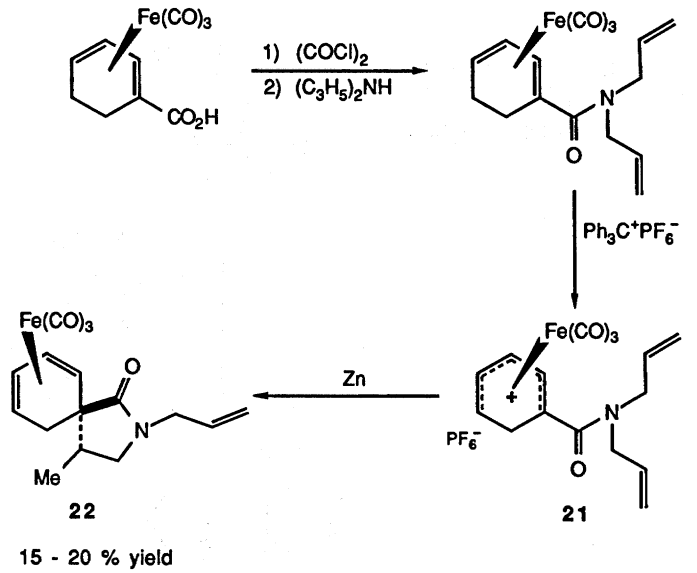


FIGURE 6. Intramolecular free radical coupling reaction with dienyliron complexes.

indeed give the cyclization product **22** but in poor yield, presumably because of capto-dative stabilization of the free radical intermediate.

In an effort to overcome these problems we investigated a new method for olefin/diene coupling. Although diene–$Fe(CO)_3$ complexes are inert to the majority of typical diene reactions, it has been observed that photochemical reaction between complexes such as **23** and electron-deficient olefins such as tetrafluoroethylene leads to products of type **24**, although in rather poor yields (Bond *et al.* 1975). We decided to investigate an intramolecular version of this reaction, and subjected the allyl ester **25** to thermal reaction conditions, giving the lactone **26** in 25–30 % yields. When this reaction is conducted under carbon monoxide atmosphere the yields are improved dramatically. Also, in several cases where unsaturated esters fail to cyclize, the corresponding amide may be used successfully, as shown in figure 7 (Pearson *et al.* 1987*b*). Although the stereochemistry at the newly formed quaternary centre in this reaction is defined

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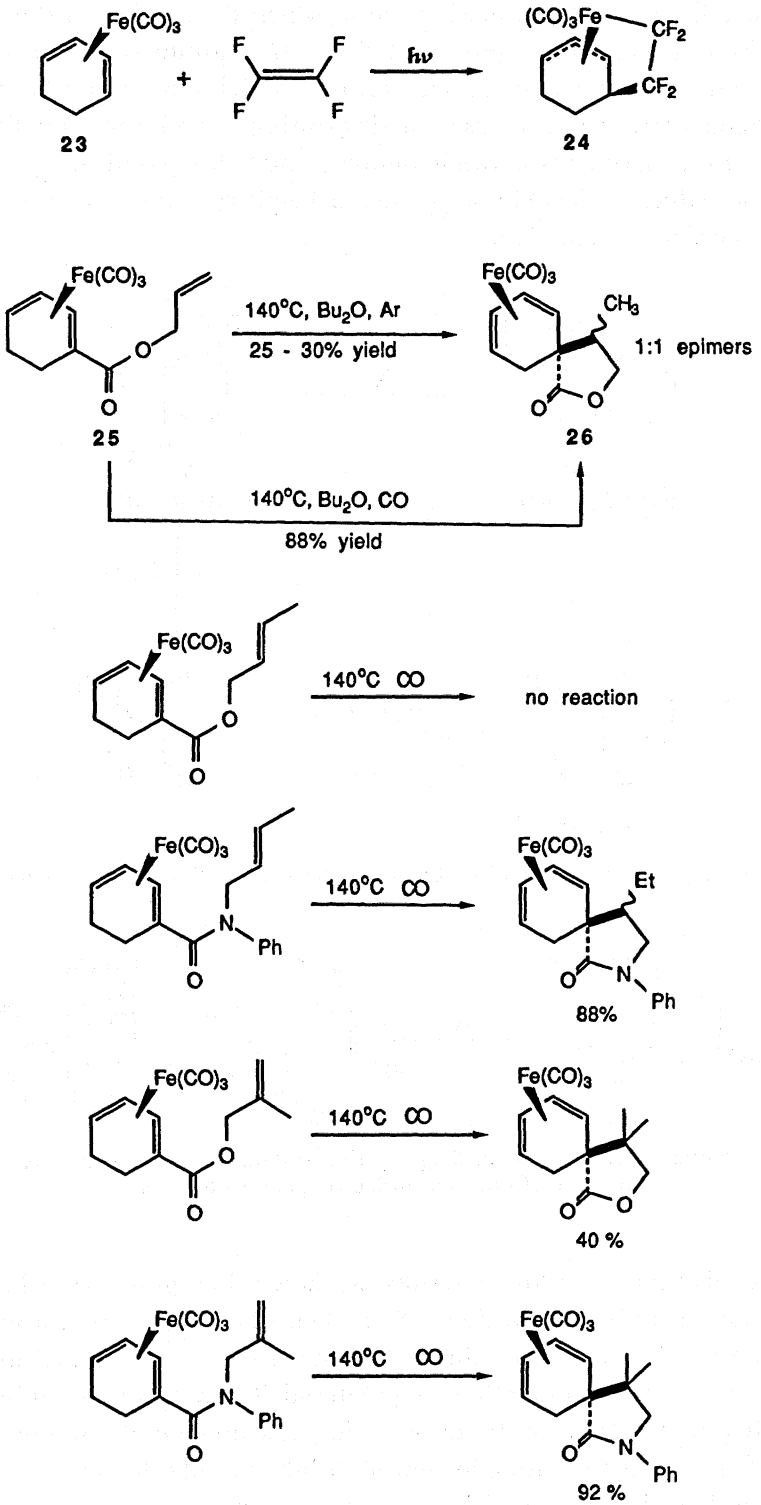


FIGURE 7. Coupling of diene–$Fe(CO)_3$ and alkene moieties.

relative to the metal, and implies a mechanism in which the pendant olefinic group becomes coordinated to iron, a mixture of epimers at the CHMe group is obtained. Based on some rather loose mechanistic arguments we felt that the ring closure should be stereospecific and suspected that diene rearrangement was occurring during and after the coupling reaction. This was supported by the experiments shown in figures 8 and 9, using optically pure and deuterium labelled precursors, which indicated that the stereochemistry of the CHMe group was partially fixed during the cyclization reaction.

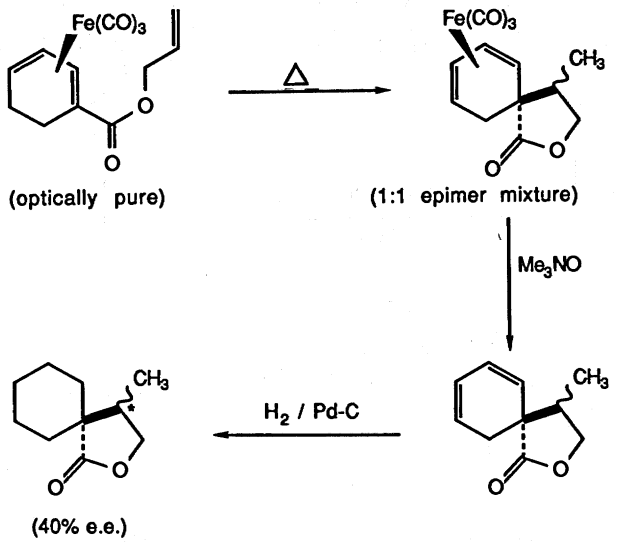


FIGURE 8. Partial racemization observed during diene–$Fe(CO)_3$/alkene coupling reaction.

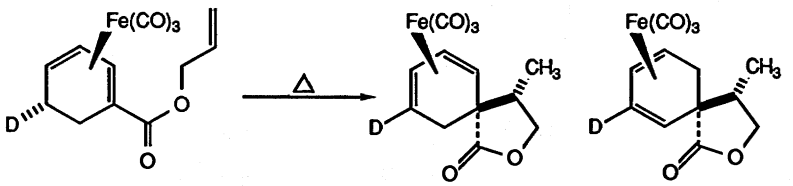


FIGURE 9. Deuterium labelling experiment showing rearrangement of diene–$Fe(CO)_3$ unit during coupling with alkene.

A plausible explanation for these results is shown in figure 10, where stereospecific cyclization is followed by 'epimerization' of the diene–$Fe(CO)_3$ group, a well-characterized process. The observed leakage of absolute stereochemistry was presumed to be caused by a competing but slower racemization of starting material. This was supported by the observation that the optically pure methyl ester **9** racemizes in a few hours under the reaction conditions, a result that we found quite surprising in view of the absence of other rearrangement products. This racemization is easily prevented by attaching a cyano group as in complex **27**, which undergoes no rearrangement and no stereochemical leakage on heating. On the other hand, complex **28** completely rearranges to **29**. We were rewarded to discover that optically pure complex **30** cyclizes to give a single complex **31** in 87% yield and 100% diastereomeric excess. NMR experiments with chiral lanthanide shift reagents indicated that this material was optically

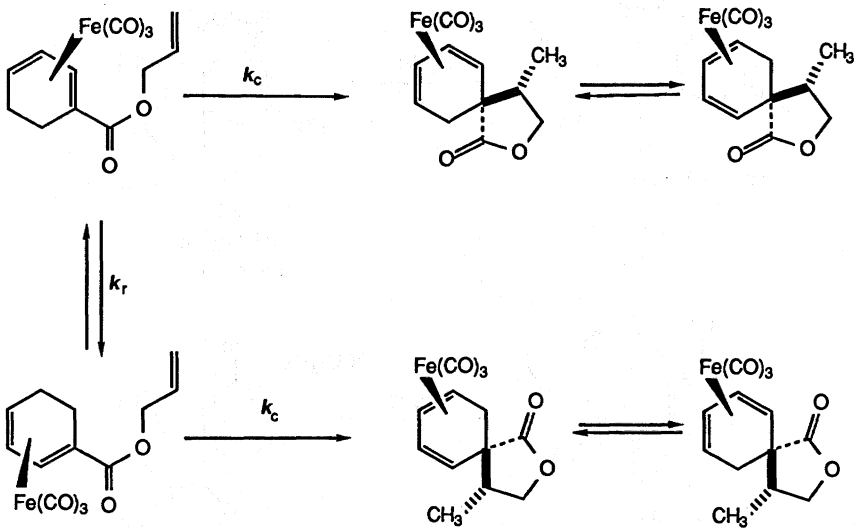
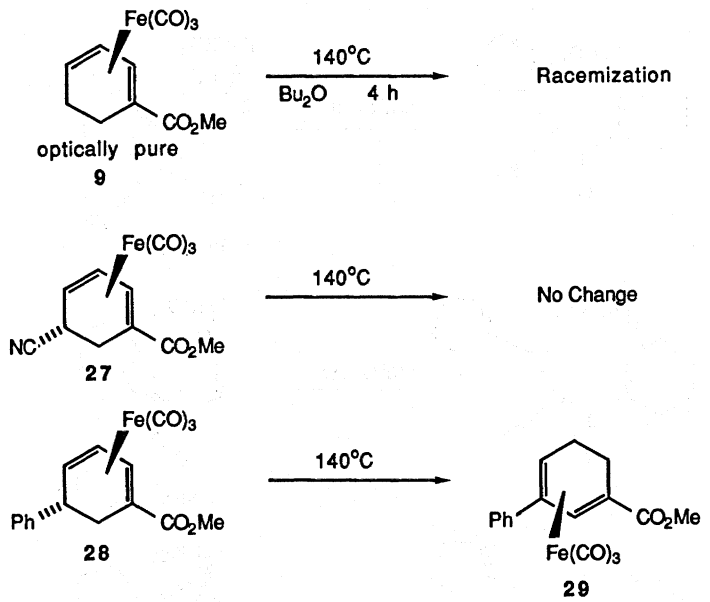


FIGURE 10. Rearrangements occurring during diene–$Fe(CO)_3$/alkene coupling reactions. (Data indicate $k_c/k_r \approx 2$.)



pure. Similarly, **32** gives **33** in 84% yield without rearrangement, so that a high degree of stereo-control is possible by making appropriate substitution on these complexes.

This reaction may be extended to give a ring-coupling reaction of potential value in trichothecene synthesis, some results being shown in figure 11. We are currently studying approaches to verrucarol synthesis based on this methodology.

More recently, we have investigated the use of cyclohexadiene–molybdenum complexes for the construction of quaternary carbon centres. The 1,4-dimethyl substituted diene complex **34** is readily prepared as shown using methodology developed by Bottrill & Green (1977). We have found that this complex reacts with a variety of carbon nucleophiles to generate

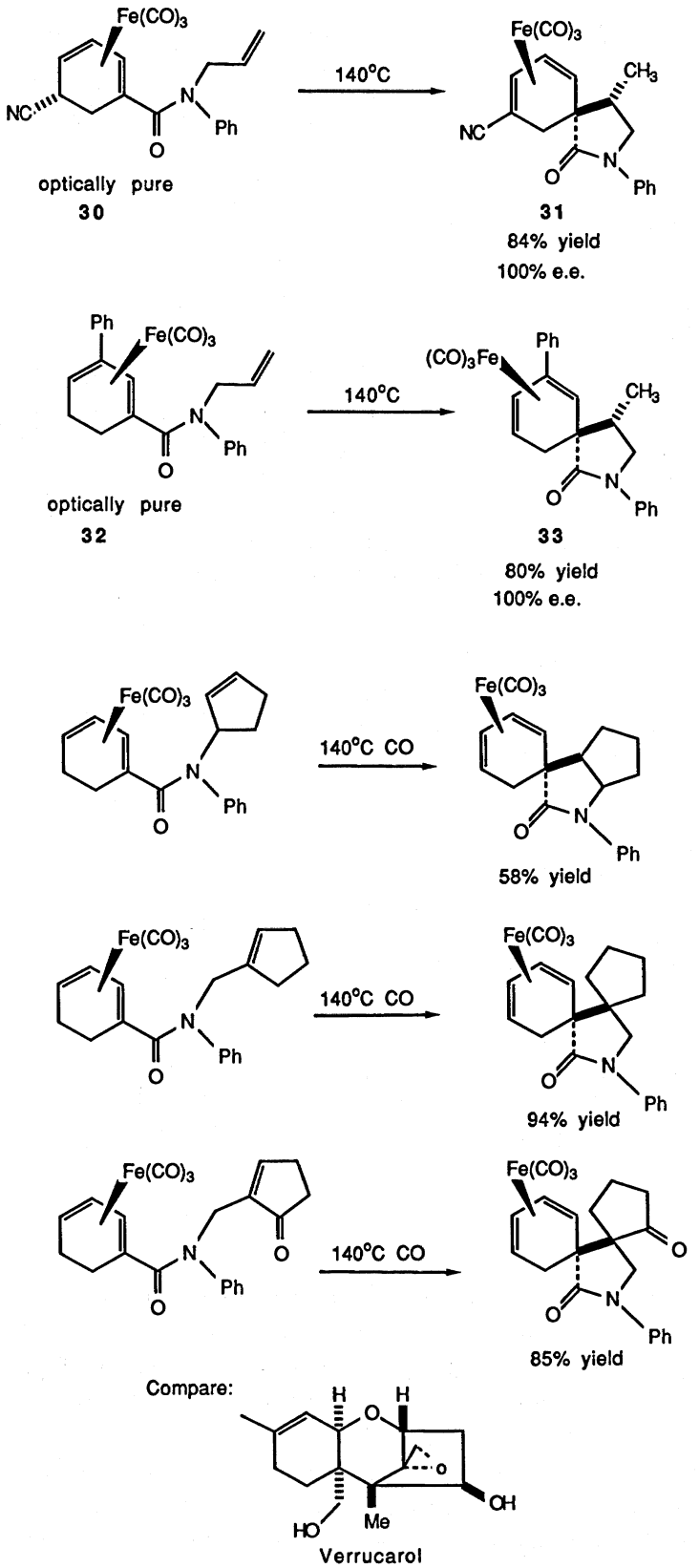


FIGURE 11. Application of diene–$Fe(CO)_3$/alkene coupling reaction to the construction of complex ring systems of the type found in trichothecenes.

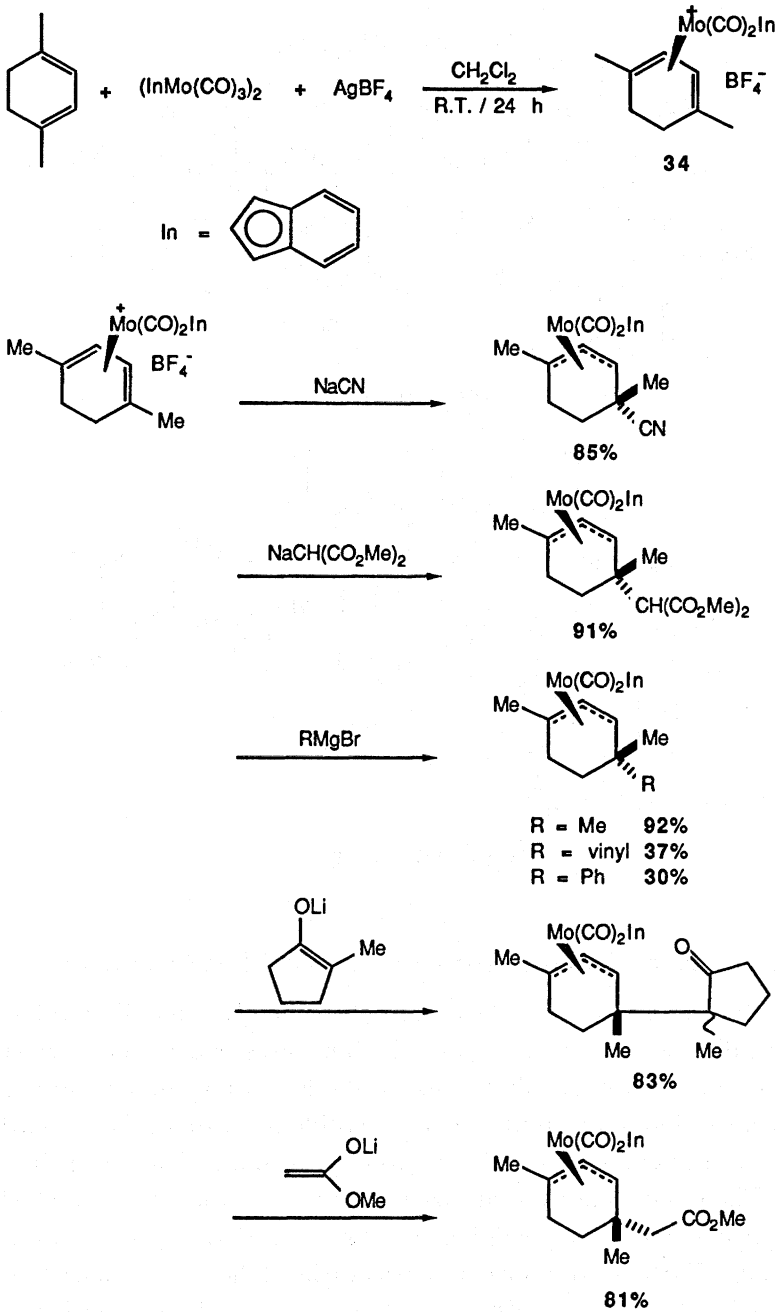
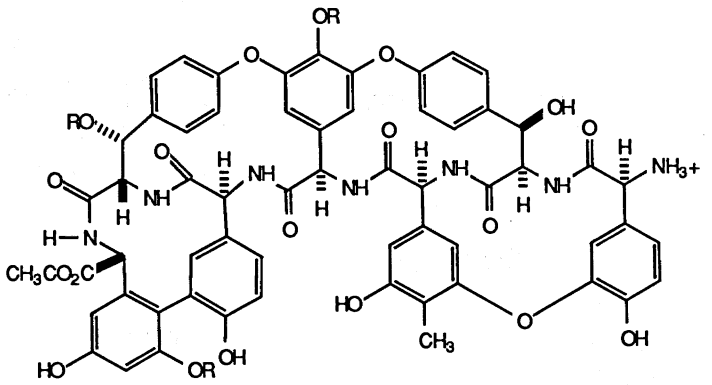
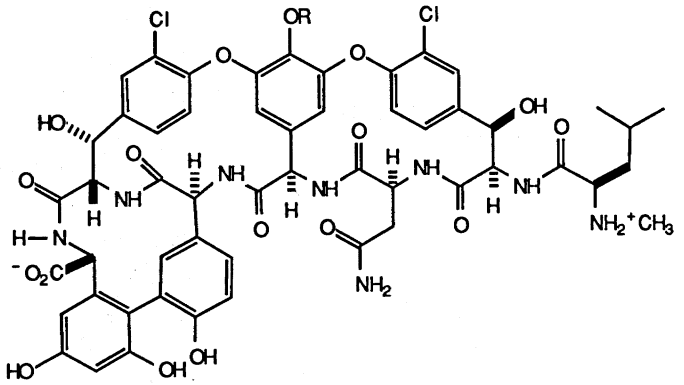


FIGURE 12. Some uses of diene–molybdenum complexes in the construction of quaternary carbon centres.

quaternary centres, as illustrated in figure 12. Particularly noteworthy are the alkylations with Grignard reagents and 'hard' lithium enolates, because the analogous reactions are unsuccessful using dienyliron complexes such as **1**. Thus, we anticipate that, provided appropriate diene–molybdenum complexes can be prepared, a wide range of natural products will be accessible using this approach.



RISTOCETIN (35)



VANCOMYCIN (36)

Synthetic applications of arene–$Mn(CO)_3$ complexes

Ristocetin A (**35**) and vancomycin (**36**) are polycyclic glycopeptide antibiotics which pose a considerable challenge in terms of synthesis. The presence of the aryl ether linkages is problematic because these are usually formed in the laboratory under quite harsh conditions that promote racemization in the amino acid or peptide substituent. We recently described the application of chlorobenzene-manganese tricarbonyl to the formation of diaryl ethers under mild conditions. These results are summarized in figures 13 and 14, from which it can be seen that protected tyrosine and 4-hydroxyphenylglycine can be *O*-arylated with no racemization (Pearson *et al.* 1986). Furthermore, unsymmetrical triaryl diethers such as **39** can be prepared with good selectivity (figure 15). Although this augers well for synthetic approaches to ristocetin and vancomycin, the methodology raises other problems. For example, the most expedient route to these molecules would be via chloroarene–$Mn(CO)_3$ complexes such as **40** in which a protected amino acid side chain is present. Unfortunately, all attempts thus far to prepare such complexes have been unsuccessful. This contrasts with arene–chromium chemistry, where we have been able to prepare complexes such as **41**, but unfortunately these are unreactive toward phenoxide nucleophiles.

We have been able to partly overcome these shortcomings by exploiting the reactivity of arene–$Mn(CO)_3$ complexes toward carbanion nucleophiles, a simple example of which is shown in figure 16. The diaryl ether complex **42** is obtained in good yield and undergoes clean

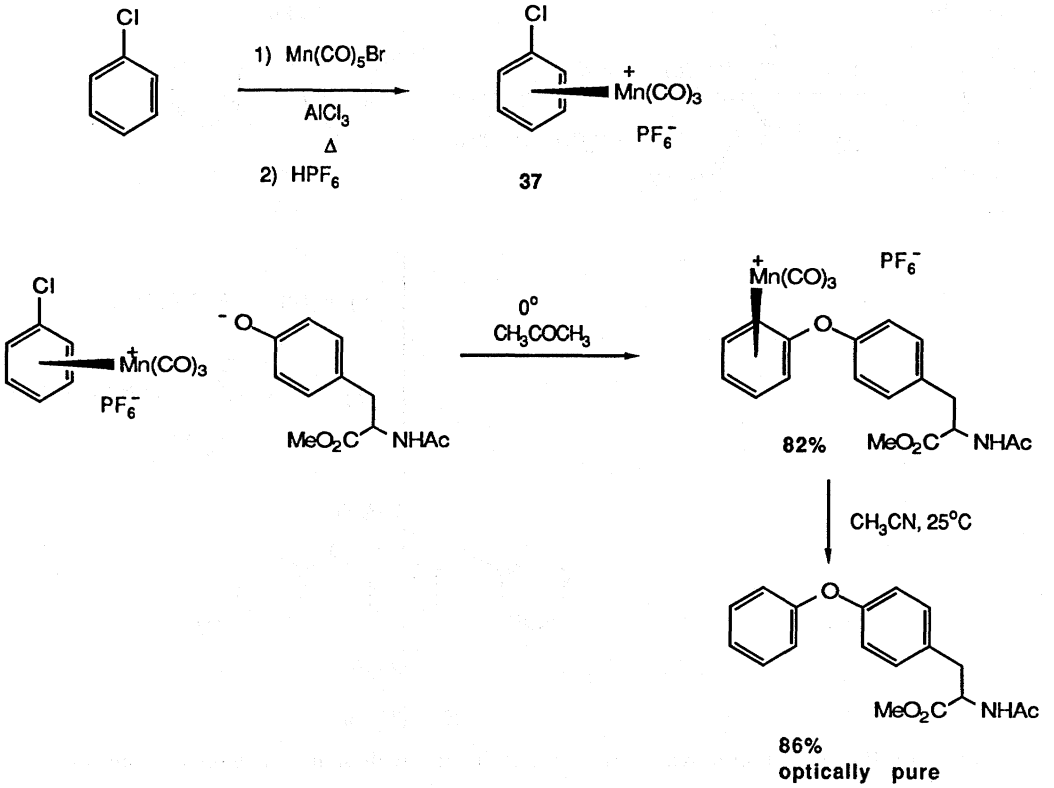


FIGURE 13. *O*-arylation of tyrosine derivatives with arene–manganese chemistry.

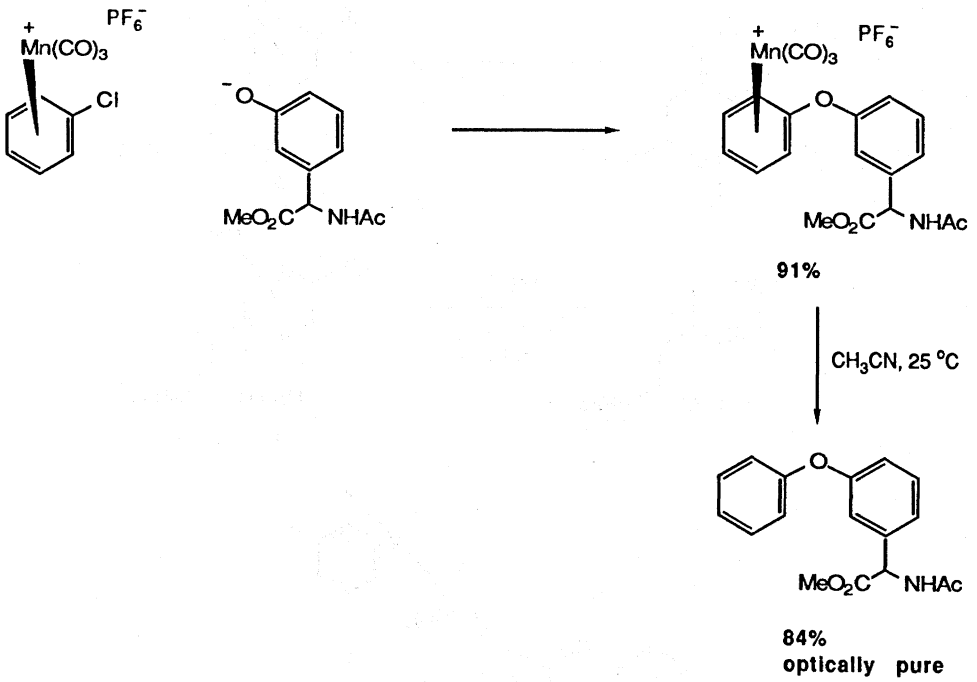


FIGURE 14. *O*-arylation of 4-hydroxyphenylglycine derivatives with arene–manganese chemistry.

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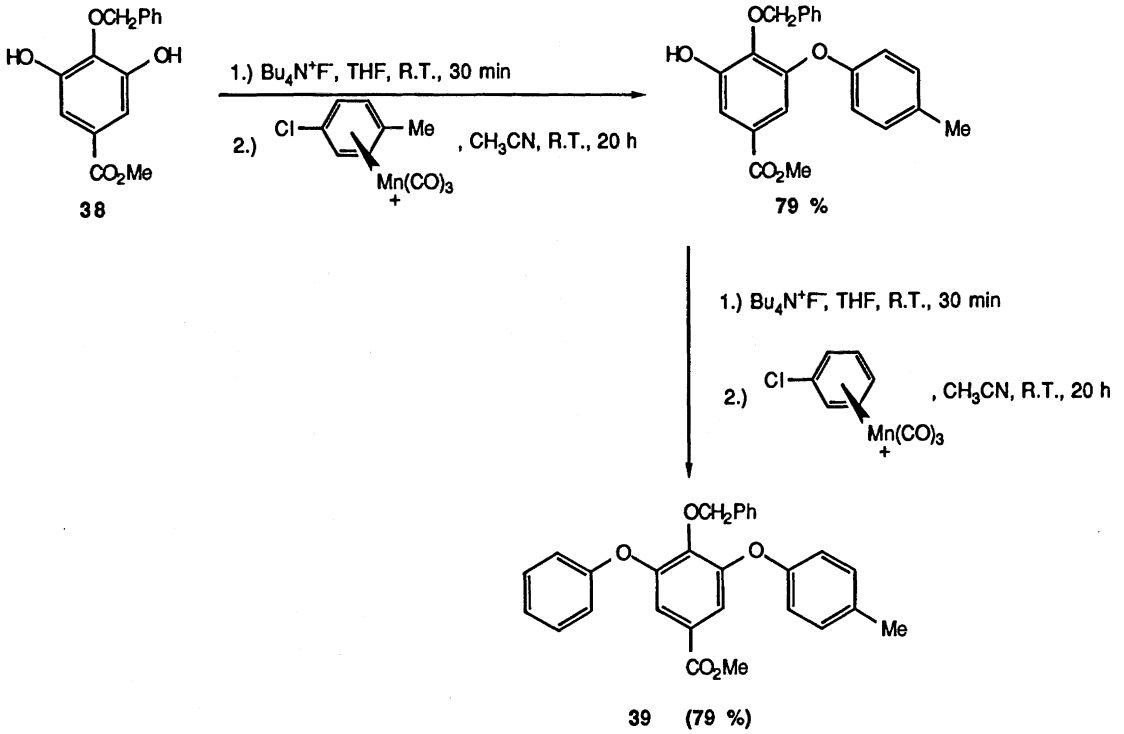
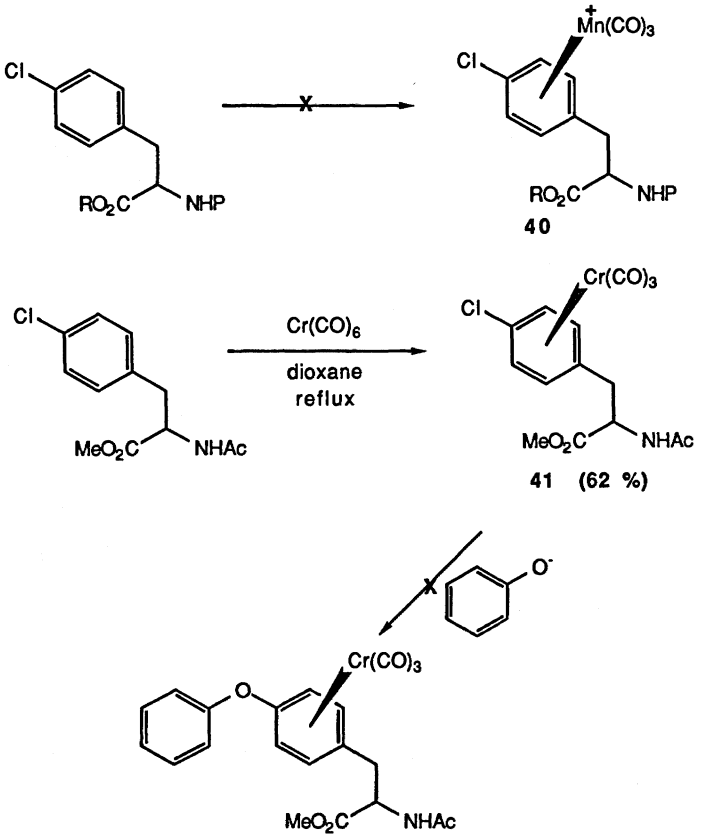


FIGURE 15. Preparation of unsymmetrical triaryl diethers with arene–manganese chemistry.



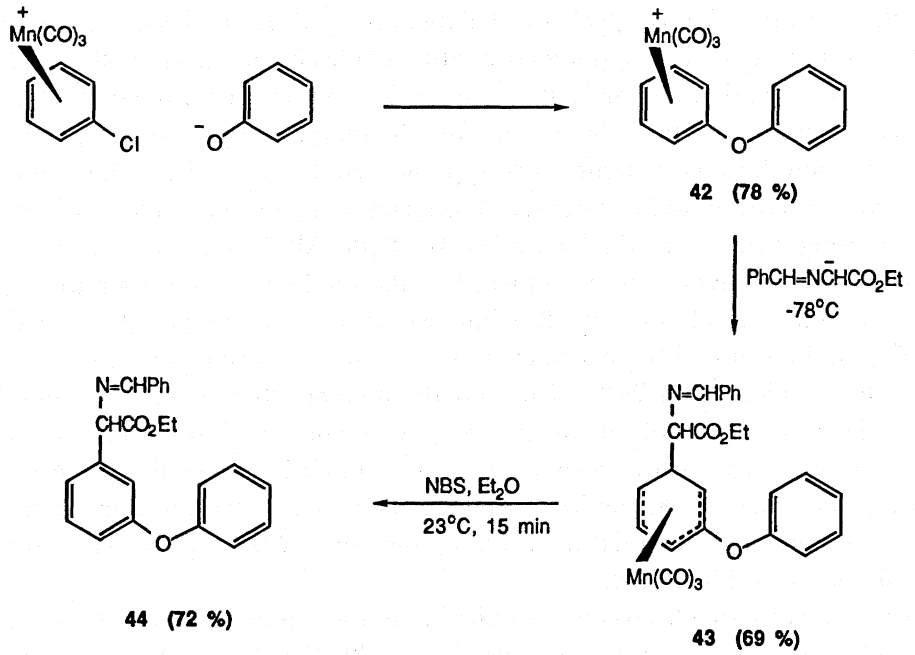
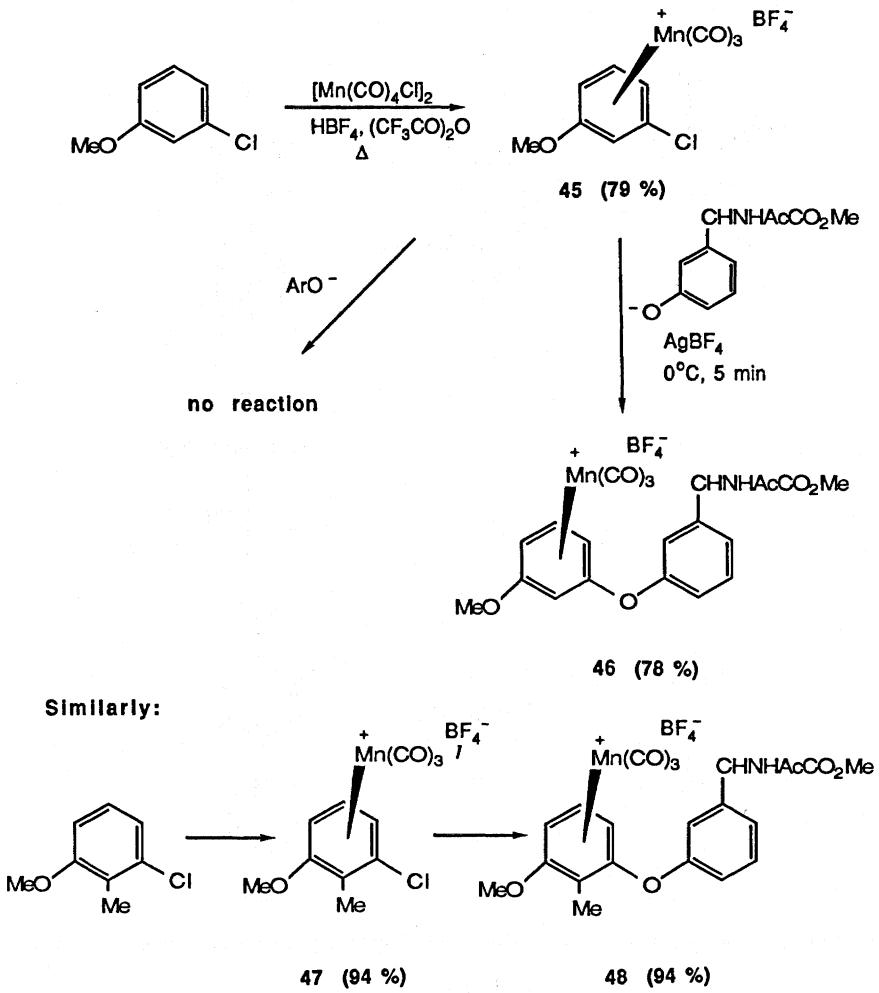


FIGURE 16. Aryl ether formation coupled with carbanion nucleophile addition to arene–$Mn(CO)_3$ complexes.



addition of the *N*-protected ethyl glycinate enolate developed by Stork *et al.* (1976), *meta* to the ether substituent to give **43** as an equimolar mixture of diastereoisomers in 69% yield. Several methods for decomplexation and aromatization of **43** were examined, the most efficient being treatment with *N*-bromosuccinimide, which gave the diaryl ether **44** in 72% yield.

The question now became whether this approach could be used for the construction of ristocetin or vancomycin subunits. Attempts to prepare manganese complexes of chloroanisole derivatives by using standard methodology ($Mn[CO]_5Br$, $AlCl_3$, heat) gave very low yields of product. Several alternatives were examined, but the method of choice for these particular complexes was that developed by Russian workers (Rybinskaya *et al.* 1984) using $[Mn(CO)_4Cl]_2$ and tetrafluoroboric acid in trifluoroacetic anhydride at reflux, which gave the *m*-chloroanisole complex **45** in 79% yield and the 3-chloro-2-methylanisole complex **47** in 94% yield. The presence of the methoxy group in these complexes leads to considerable deactivation of the ring toward phenoxide attack and direct reaction of **45** with such nucleophiles gives none of the desired product. However, incorporation of silver tetrafluoroborate into the reaction mixture leads to the successful preparation of diaryl ether complexes **46** and **48** in high yield.

The next task was to attach glycine subunits in an asymmetric manner. It was found that Schöllkopf's glycine enolate equivalent derived from **49** (Schöllkopf *et al.* 1981) reacts with benzene–$Mn(CO)_3$ to give complex **50** in good yield and high diastereomeric excess. This

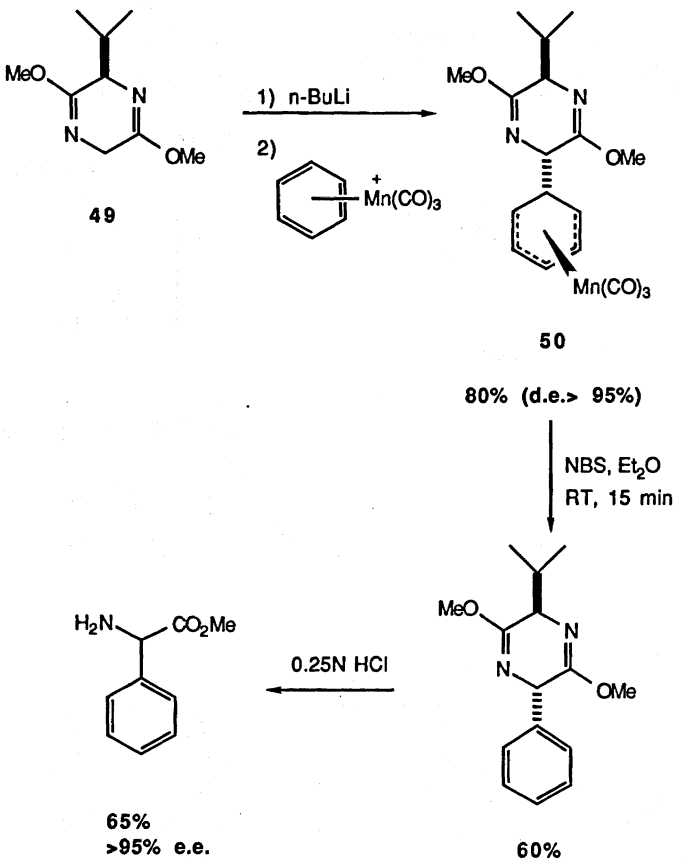


FIGURE 17. Synthesis of optically active methyl phenylglycinate with arene–magnanese chemistry.

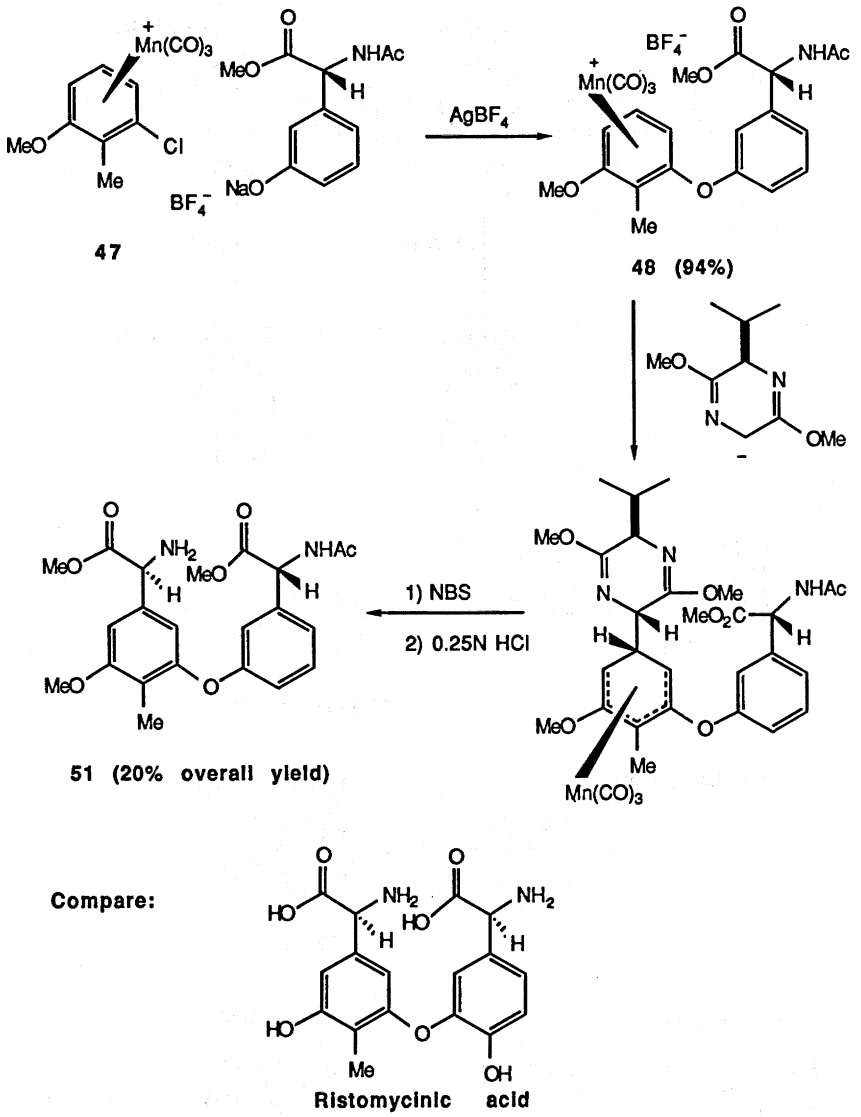


FIGURE 18. Illustration of potential application of arene–manganese chemistry for synthesis of ristomycinic acid derivatives.

could be converted to phenylglycine methyl ester in good overall yield and with high enantiomeric excess (figure 17). This methodology can be used for the construction of ristocetin subunits, as illustrated in figure 18. Thus, complex **48** undergoes selective reaction with the chiral glycine enolate equivalent **49** to give **50** with good selectivity, and decomplexation followed by unmasking of the glycine side chain gives the diaryl ether **51** in 20% overall yield from **48**. Clearly, use of a suitably protected 3,4-dihydroxyphenylglycine derivative in the ether formation will allow a synthesis of ristomycinic acid and this is currently being studied in our laboratory. The major problem with the sequence appears to lie in the conversion of **48**, because we have observed the formation of product corresponding to loss of the $Mn(CO)_3$ group from **48**. Presumably, this is a result of carbanion attack at the manganese, and we are examining methods of overcoming the problem. In this respect, we have found that silyl enol ethers give cleaner reactions and this avenue will be explored further.

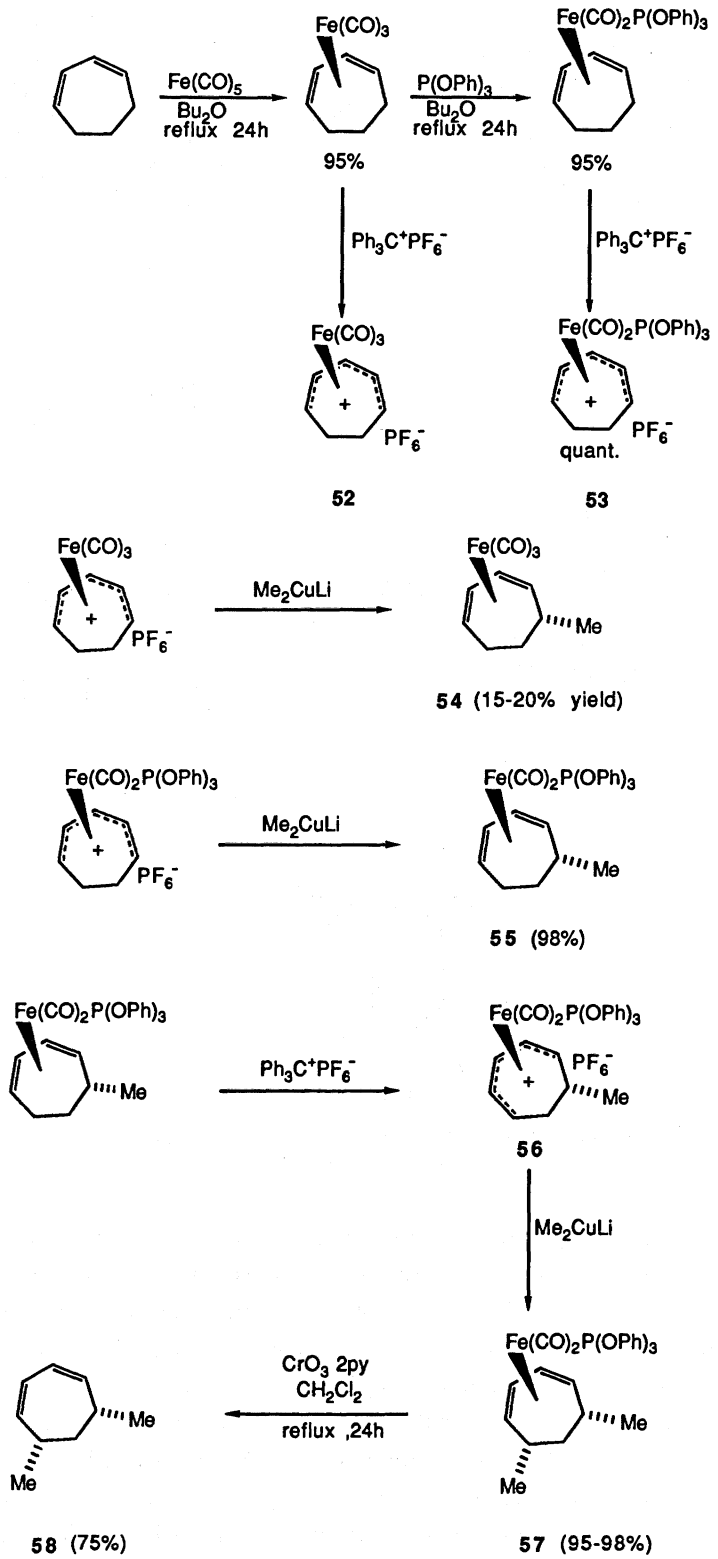


FIGURE 19. Preparation and reactions of cycloheptadienyliron complexes.

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Multiple stereochemical control with dienyliron complexes

Addition of carbon nucleophiles to dienyliron complexes generally occurs stereospecifically *trans* to the metal. This stereocontrol may be used to control the sequential formation of several carbon–carbon bonds, provided the process of nucleophile addition and reactivation of product can be realized. We have studied this approach to stereocontrol with cycloheptadienyliron complexes, the preparation of which is illustrated in figure 19. Although the simple dienyliron tricarbonyl complex is readily prepared, it does not react cleanly with a wide range of carbon nucleophiles to be of much synthetic utility. Thus, reaction of **52** with dimethylcopperlithium gives **54** in low yield, and many by-products are observed. On the other hand, the triphenylphosphitedicarbonyl derivative **53** is easily prepared and is well-behaved towards carbon nucleophiles. In this way, **55** can be efficiently prepared on large scale. Hydride abstraction from **55** proceeds smoothly to give **56**, which undergoes a second nucleophile addition at the less-hindered dienyl terminus to give **57** (Pearson *et al.* 1984). Decomplexation of **57** gives the diene **58**.

Asymmetric functionalization of the diene of **58** is possible by 1,4-oxidation coupled with stereospecific enzymatic hydrolysis of the diacetate **59** (figure 20). In this manner the intermediate **60** can be produced in 100% enantiomeric excess. Reaction of **60** with dimethylcopperlithium occurs stereospecifically to give **61**, and cleavage of the double bond followed by desilylation leads to the (+)-Prelog–Djerassi lactone (**62**), which has been the object of considerable synthetic endeavour in recent years, a good summary of which is given by Martin & Guinn (1987).

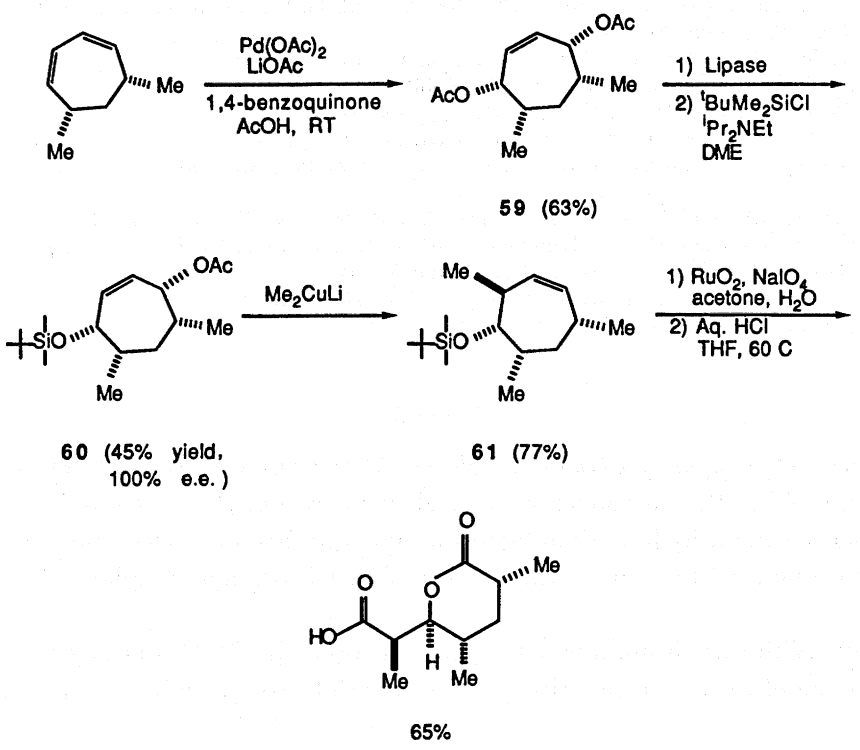

Figure 20. Asymmetric synthesis of (+)-Prelog–Djerassi lactone.

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Discussion

L. S. Hegedus (*Department of Chemistry, Colorado State University, U.S.A.*). Professor Pearson showed the use of $NOPF_6$ to convert a neutral metal carbonyl to a cationic metal nitrosyl, thereby activating the π-hydrocarbon ligand to undergo further nucleophilic attack. Can the same procedure be used to activate (arene)chromiun tricarbonyl complexes?

A. J. Pearson. With this chromium system, the reaction with NO^+ is not clear, and although in principle it should work, in practice it is not a useful procedure in this system.