

NATURAL PRODUCTS SYNTHESIS USING ORGANOIRON COMPLEXES

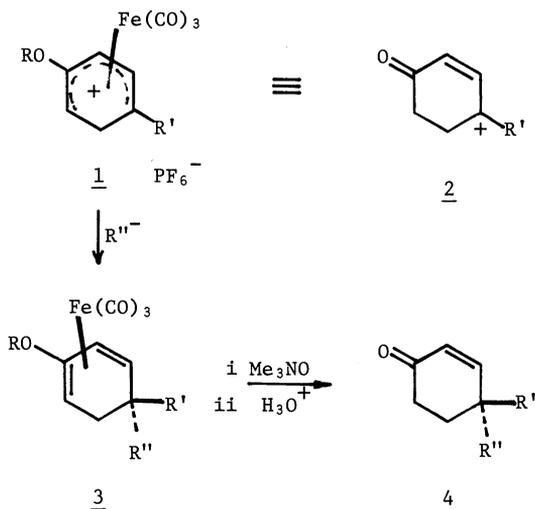
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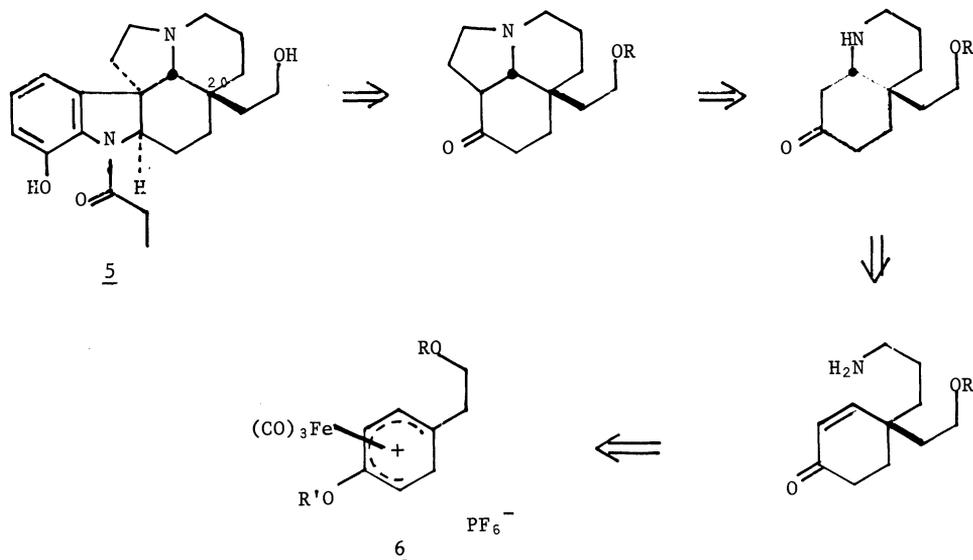
Abstract - A survey is presented of applications of dienyl-Fe(CO)₂L complexes as intermediates for natural products synthesis, based on (a) complexes which act as cyclohexenone γ -cation equivalents, and (b) the ability of the metal to direct stereochemistry of C-C bond formation in seven-membered rings.

This paper provides the opportunity to give a brief review of some of our work carried out at Cambridge University, England, during 1981-82, together with a progress report on some new projects which were initiated in October 1982, subsequent to moving to Case Western Reserve University. The work at Cambridge was based on the utilisation of cyclohexadienyl-Fe(CO)₃ complexes of type 1 which we have now established as synthetic equivalents of cyclohexenone- γ -cations (1), e.g. 2. Thus, reaction of 1 with nucleophiles usually occurs regioselectively to give complexes of type 3, which are readily converted to cyclohexenones 4.

It is appropriate to discuss the application of this concept to a total synthesis of the Aspidosperma alkaloid (\pm)limaspermine 5, since this piece of work illustrates a number of interesting aspects of reactivity, and methods which can be used to control regioselectivity during manipulation of diene and dienyl complexes of iron (2).

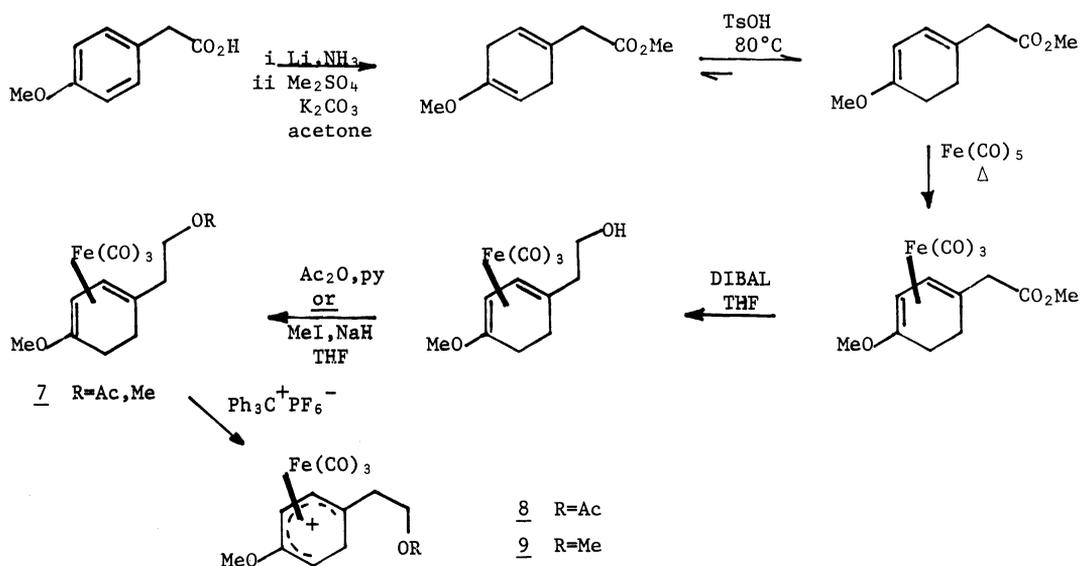


First let us take a look at the retrosynthetic analysis of limaspermine which will enable us to utilise a cyclohexenone- γ -cation equivalent, shown in Scheme 1. This analysis is based on the original concept used by Stork (3) for the synthesis of the related alkaloid (\pm)-aspidospermine, which lacks the oxygen functionality in the C-20 substituent. Thus, it can be seen that a suitable starting point is a complex of type 6, with variable groups R and R'. It will be seen that the choice of these groups is very important.



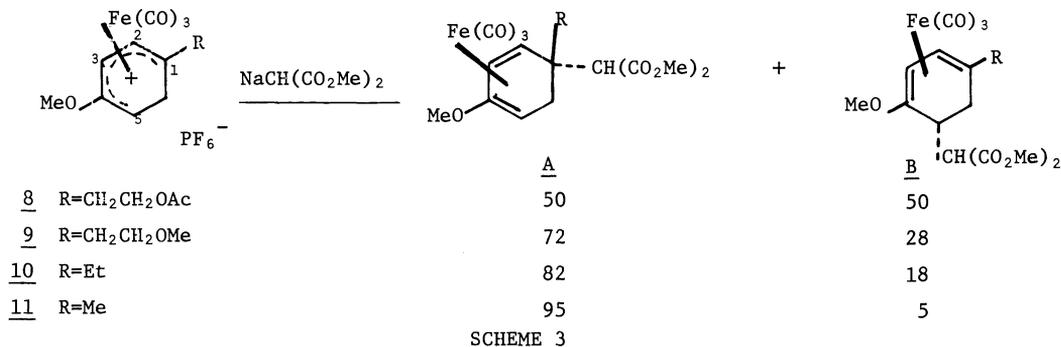
SCHEME 1

Since 4-methoxyphenylacetic acid is readily available, this seemed like a useful starting material for the preparation of a complex of type 6. Scheme 2 shows the preparation of two possible complexes 8 and 9. It may be noted that the hydride abstraction from diene-Fe(CO)₃ complexes to give 8 and 9 is highly regioselective, giving ca 90% yield of the desired materials (4). We have attributed this directing effect to the preferential formation of the dienyl cation having a high HOMO energy level and a low LUMO energy level, thereby leading to a stronger synergic interaction with the metal. It may be noted that the preferred cation does not correspond to the more stable uncomplexed cation (witness the ortho/para directing effect of alkoxy substituent during aromatic electrophilic substitution)(1).



SCHEME 2

It was proposed to introduce the necessary 3-aminopropyl side chain by addition of malonate at C-1 of 8 or 9, followed by decarboxylation, homologation and functional group manipulation. At this point, an interesting observation was made concerning regioselectivity of nucleophile addition to complexes 8 and 9 summarised, together with other results for comparison in Scheme 3.

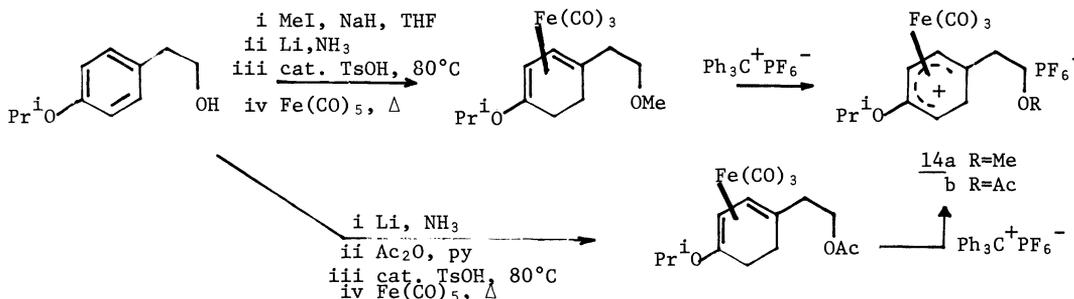


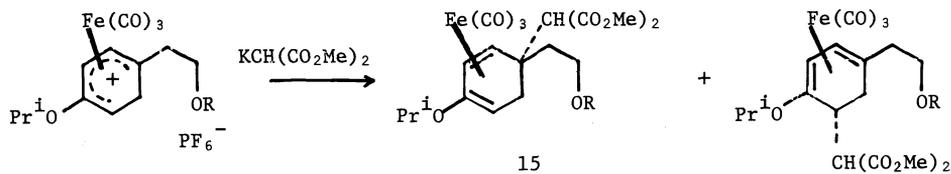
Thus, products of nucleophile addition to either diene terminus are obtained for complexes 8, 9 and 10, whereas very high regioselectivity is observed for the simple complex 11. Whilst we might have expected poorer regioselectivity for 10 compared to 11, due to increased steric bulk of the C-1 substituent (R), the changes observed in going from 10 to 9 to 8 are not yet rationalised. If we were to devise an efficient synthesis of an appropriate 4,4-disubstituted cyclohexenone, then it was clear that the regioselectivity of this reaction must be improved. With a good supply of complex 10 in hand, we carried out a series of experiments to determine whether subtle alterations in the nucleophile would significantly affect regioselectivity. Surprisingly, it was found that the ratio of products A:B was dependent upon the nature of the cation associated with the malonate enolate, as shown in Table 1 (5).

TABLE 1. Product ratios from reaction of complex 10 with MCH(CO₂Me)₂

M	Ratio A:B
Li	3.0
Na	4.6
K	5.6
Na/18-crown-6	5.7

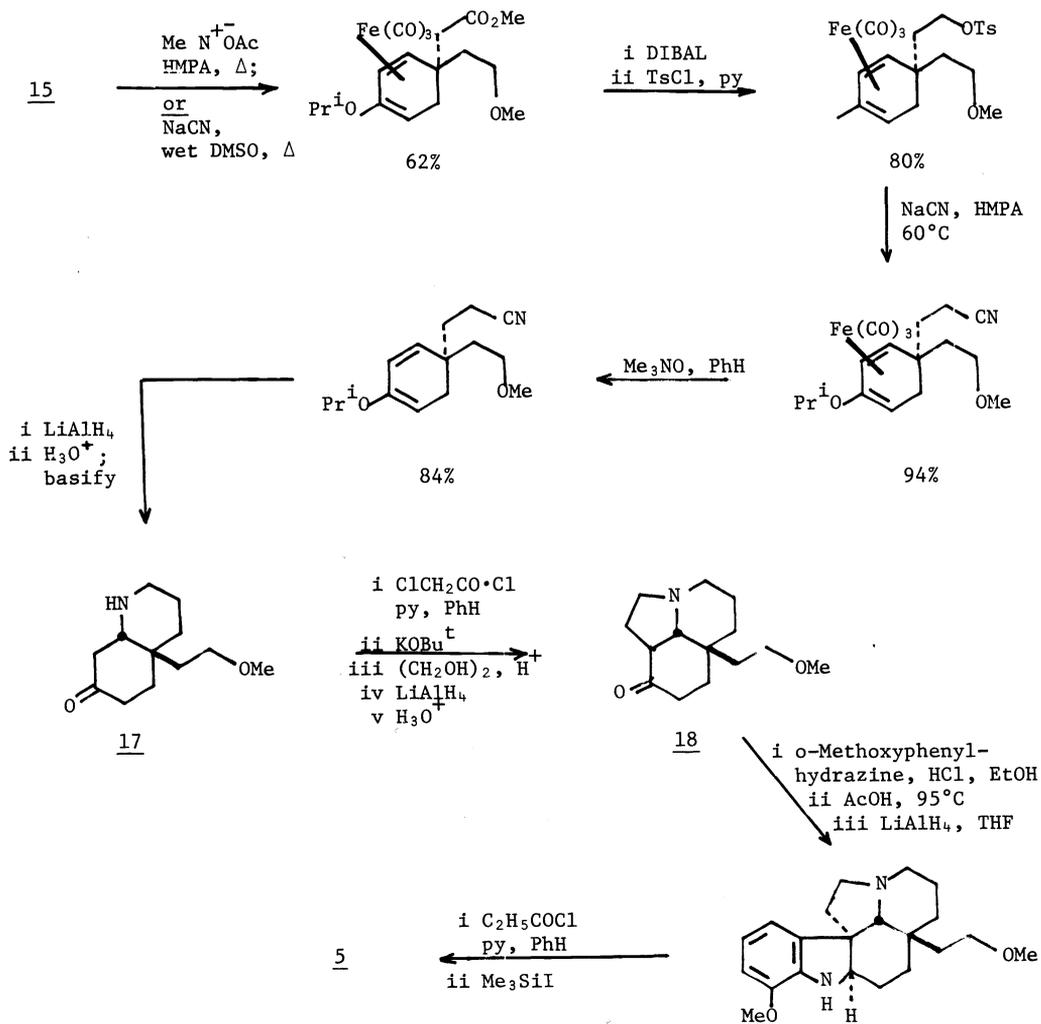
Thus, the lower the energy of the metal enolate HOMO (6), the poorer the selectivity for the C-1 terminus of 10. Best results are obtained using the potassium enolate, but a mixture is still produced. Consequently, we decided to try and improve this still further by replacing the 4-methoxy group of 9 and 10 with *iso*-propoxy. Whilst the size of the latter might give better nucleophile addition results, there was still the question of how a larger group would affect the regioselectivity of hydride abstraction. In the event, the directing effect shown by alkoxy substituent during the latter reaction led to formation of the desired diene complexes 12 and 14 quantitatively. Addition of dimethyl potassiummalonate to 12 gave quantitative yield of 13 as a crystalline compound, whilst 14a gave a 10:1 mixture of 15 and 16, as shown in Scheme 4. The corresponding acetate diene complex 14b gave a 6:1 mixture of "regioisomers" on reaction with dimethyl potassiummalonate (7), so we chose to use the methyl ether 14a for the limaspermine synthesis.





SCHEME 4

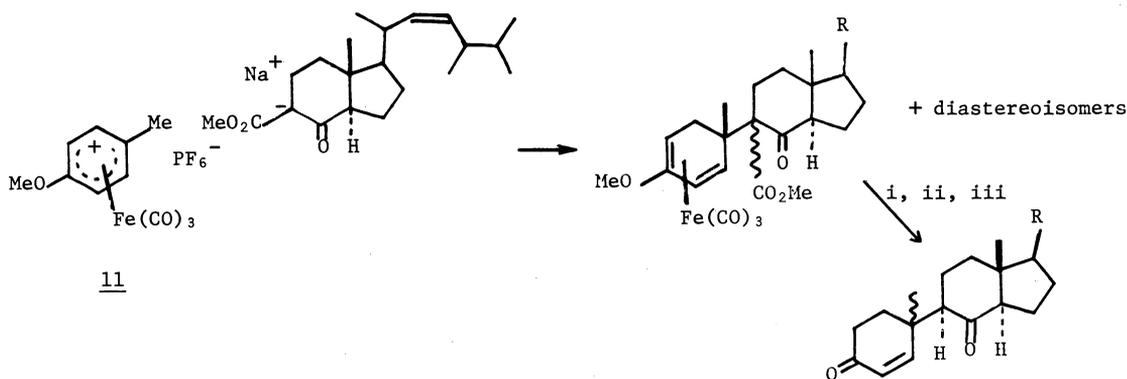
The complex **15** thus obtained serves as a useful intermediate for the synthesis of (\pm)-limaspermine and its elaboration reveals yet another interesting aspect of diene- $\text{Fe}(\text{CO})_3$ chemistry, viz, the wide range of chemical transformations which may be carried out in the presence of the metal and its removal at a desired stage in the synthesis. The sequence is shown in Scheme 5, in which the decahydroquinoline **17** is produced and then elaborated to the target molecule using Stork's approach.



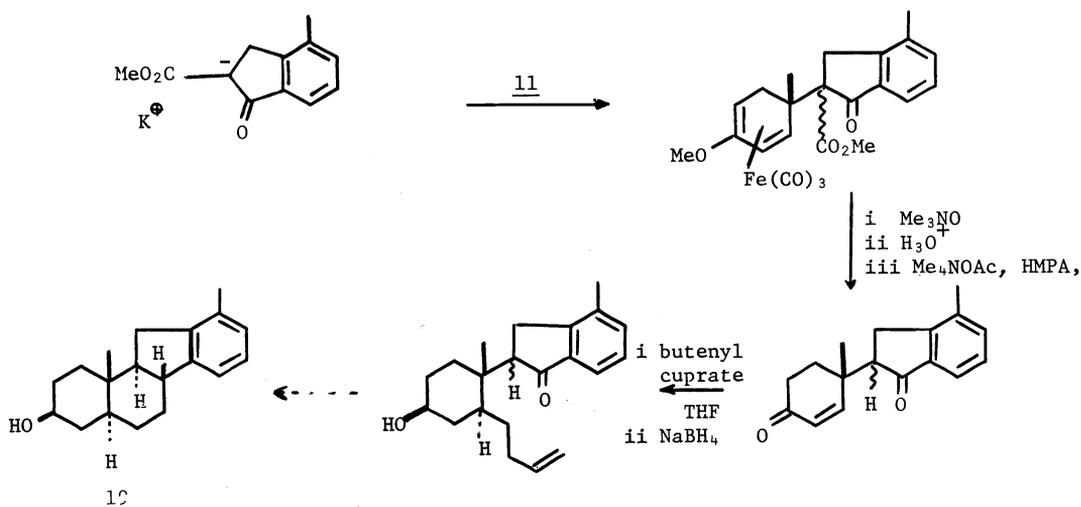
SCHEME 5

This synthesis illustrates how the concept of cyclohexenone γ -cation equivalents can be used in an actual synthesis and, equally important, shows how problems associated with regioselectivity of nucleophile addition can be overcome.

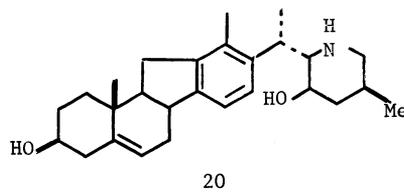
As was mentioned earlier, the methyl-substituted cyclohexadienyl complex 11 is very well-behaved during nucleophile addition. We have previously described its regioselective reaction with enolates of keto esters derived from cyclopentanones, cyclohexanones and tetralones. More recently we have commenced investigations into some potentially convergent syntheses of steroids and C-nor-D-homosteroids. The latter ring system, exemplified by compound 19, forms the basic carbon framework for Veratrum alkaloids exemplified by the simplest member veratramine 20, and which are potentially useful antihypertensive compounds (8). Our preliminary studies in these areas are summarised in Schemes 6 and 7. The keto ester nucleophile used in Scheme 6 is readily obtained by methoxycarbonylation of an analogue of the Windaus and Grundmann ketone, in turn produced by oxidation of Vitamin D₂ (9). So far we have shown that the enolate reacts satisfactorily with complex 11 to give a mixture of four diastereoisomers. However, removal of iron, followed by enol ether hydrolysis and decarboxylation gives a mixture of two diastereoisomeric enones, since equilibration at C-9 (steroid numbering) is now possible. We are currently investigating methods for the introduction of the ring B residue. Similarly, an advanced enone intermediate for C-nor-D-homosteroid synthesis has been produced (Scheme 7). Again, we have to introduce a ring B residue and this is currently being pursued. So far the most useful approach appears to be via use of butenyl cuprate reagents.



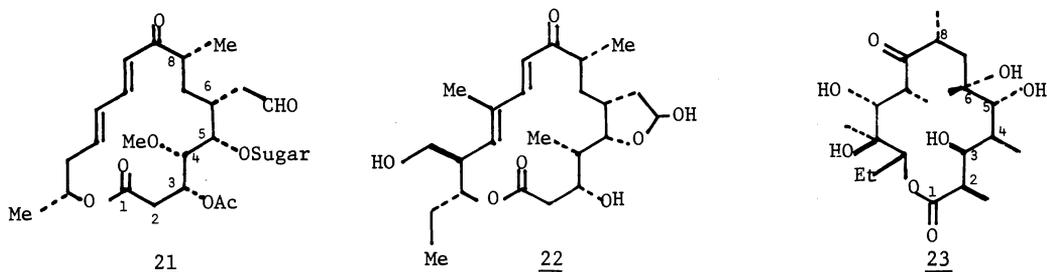
SCHEME 6 Reagents: i, Me₃NO; ii, H₃O⁺; iii, Me₄N⁺OAc, HMPA, Δ .



SCHEME 7

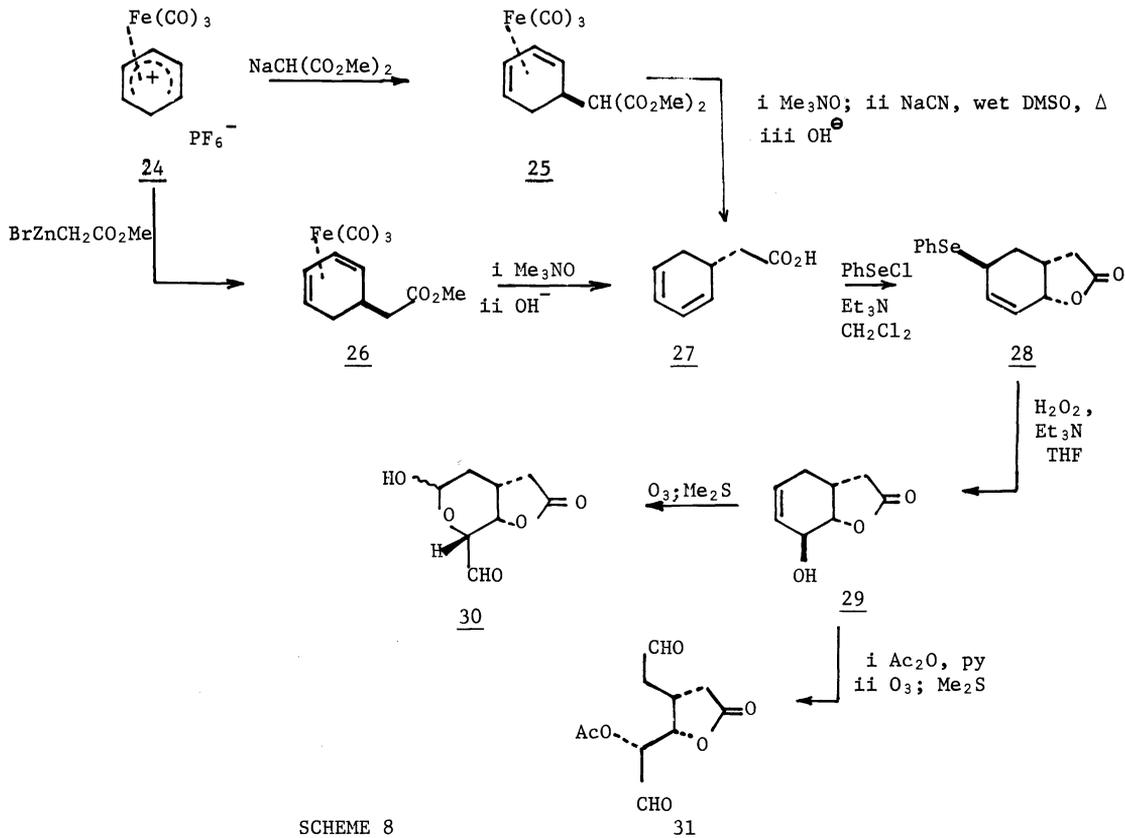


Since moving from Cambridge our interest has also been diverted towards the application of diene- $\text{Fe}(\text{CO})_3$ complexes as potential precursors for the synthesis of a variety of macrolide antibiotics. In particular, the targets in which we are currently interested are magnamycin B (10), 21, tylonolide (11), 22, the aglycone of tylosin, and erythronolide A (12), 23.



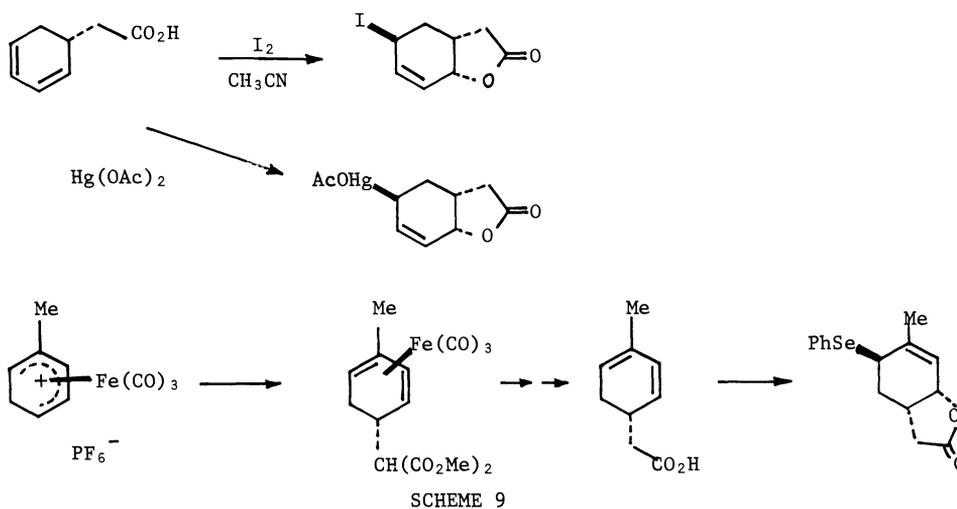
It should be stressed at this point that we are more concerned with synthesising appropriate sub-units of these compounds, using a combination of organoiron chemistry and subsequent manipulation of the organic products. This has led to the development of some novel and useful lactonisation reactions as well as to a major development of the chemistry of cycloheptadienyliron complexes. First, let us examine a potential application of cyclohexadienyliron hexafluorophosphate 24, the first dienyliron complex to be prepared.

Reaction of 24 with dimethyl sodiomalonate gives 25 in quantitative yield, which can be converted to the cyclohexadienylacetic acid 27 in good yield (Scheme 8). Alternatively, we have found that 24 reacts with the Reformatsky reagent, $\text{BrZnCH}_2\text{CO}_2\text{Me}$, to give monoester 26 which can be converted to 27, thereby avoiding a decarboxylation step. Phenylselenolactonisation of 27 gives only one γ -lactone in greater than 90% yield, shown to have the structure and stereochemistry 28 by X-ray analysis (13). Mild oxidation of the selenolactone produced the alcohol 29, by [2,3]-sigmatropic rearrangement of the intermediate selenoxide. This compound could be ozonolysed directly to give the hemi acetal 30, or converted to the acetate which could then be ozonolysed to give 31. This sequence of transformations establishes the relative stereochemistry at C-4, C-5 and C-6 in magnamycin B.

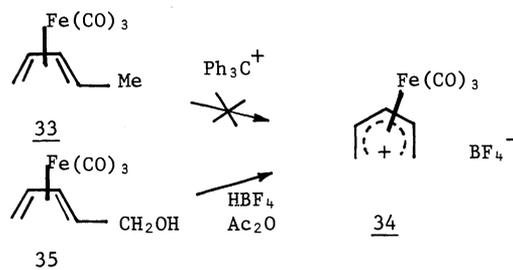


SCHEME 8

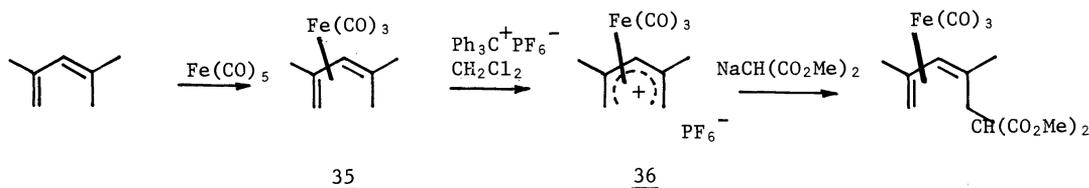
Other lactonisation reactions proceed in a similar manner, as does the lactonisation of the methyl-substituted derivative 32, shown in Scheme 9.

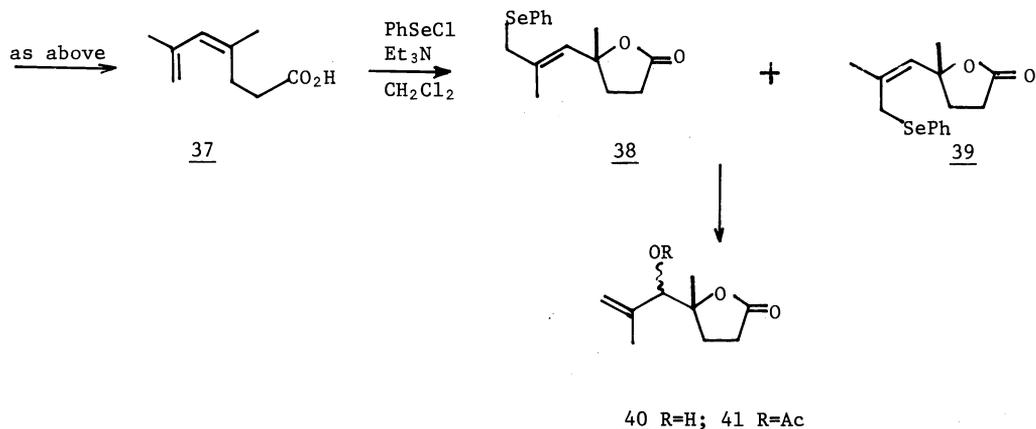


Use of the $\text{Fe}(\text{CO})_3$ group also provides an opportunity to functionalise acyclic dienes, although in most simple cases problems arise in hydride abstraction (14) due to the stereochemistry of the complex. For example, treatment of complex 33 does not produce any dienylium salt 34, but this compound can be obtained by acid treatment of 35.



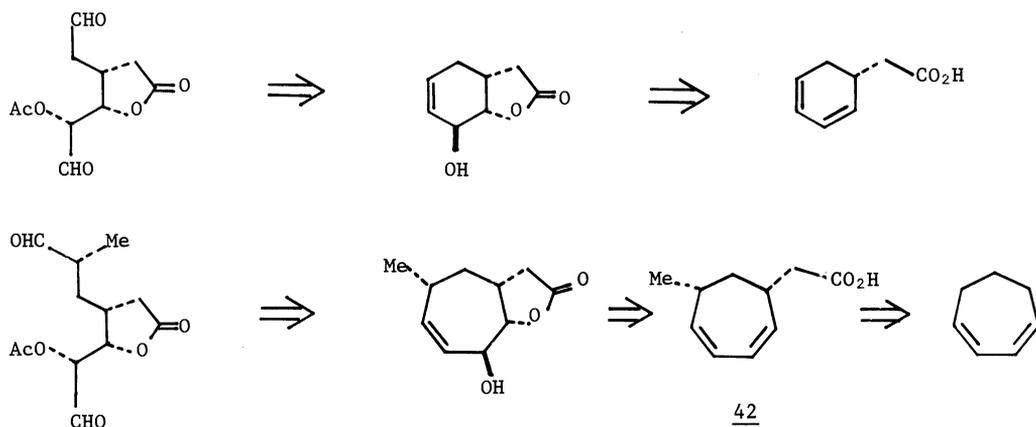
Since this approach has not been used to obtain molecules which can be further applied to organic synthesis, we investigated the functionalisation of 2,4-dimethylpentadiene, a readily available compound. The tricarbonyliron derivative 35 is formed in good yield, and converted to the dienylium salt 36 (Scheme 10). Use of an identical sequence of reactions to that described above leads to the dienylium acetic acid derivative 37, which can now be subjected to phenylselenolactonisation. Again, this occurs regioselectively and stereoselectively to give an inseparable 4:1 mixture of E and Z isomers 38 and 39. The double bond geometry of the major isomer was established by ^1H n.m.r. n.o.e. difference spectroscopy. Mild oxidation of the mixture of 38 and 39 gave an allylic alcohol 40 which appeared to be a single compound by t.l.c. and 60 MHz n.m.r. The derived acetate 41 showed two very close acetate CH_3 singlets in the 200 MHz n.m.r. spectrum (major, δ 2.092; minor, δ 2.075) indicating a 3:2 mixture of stereoisomers. In terms of overall structure, the product 40 may be useful as a C(3) - C(10) subunit of erythronolide A 23, although there are still a number of stereochemical features to be considered, and this will form the basis of future work in our laboratory.





SCHEME 10

We next turned our attention to the problem of stereospecifically introducing the 8-methyl substituent of tylosolide **22** and magnamycin B **21**. Whilst we can envisage methods of converting intermediate **31** with some degree of stereoselection to an intermediate possessing the 8-methyl substituent, the required manipulations would be cumbersome. We therefore considered the possibility of introducing the required groups at an earlier stage, using a transition metal moiety to direct the stereochemistry. From the comparative retrosynthetic analysis given in Scheme 11 we can see that ideally we require a seven-membered carbocyclic ring precursor **42**, assuming that this can be functionalised in a similar manner to the cyclohexadiene derivative **27**. Based on this analysis we have set out to establish methods for the stereospecific construction of **42**, and related molecules, commencing with cycloheptadiene.

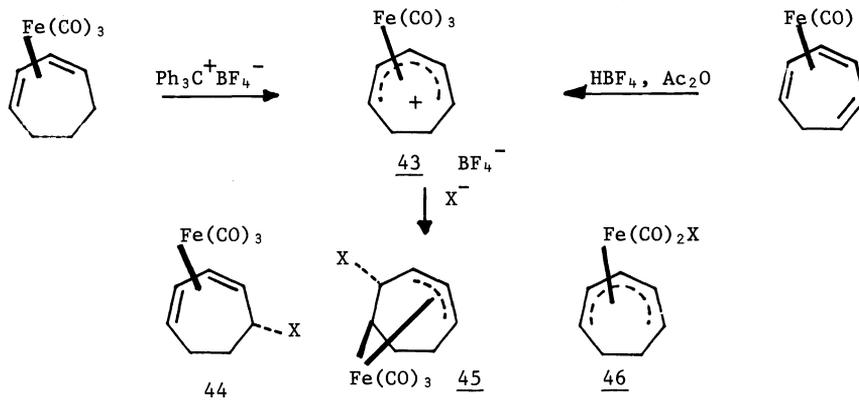


SCHEME 11

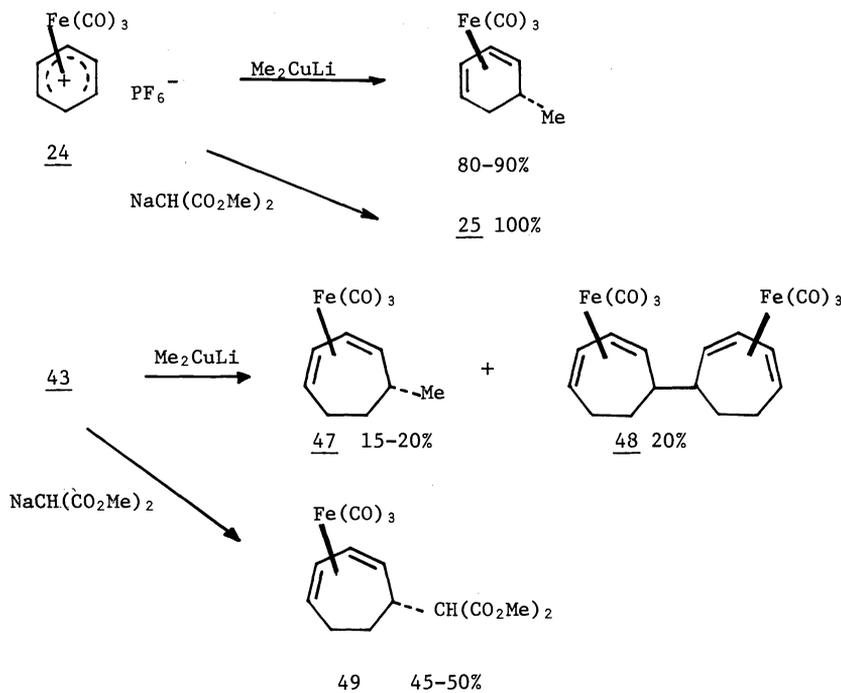
We considered that this approach would be useful in several respects. Firstly, seven-membered carbocycles have not been widely employed in complex organic synthesis (15), so that, if successful, our approach would present a number of useful opportunities for further work. Secondly, very little in terms of conformational dependence of reactivity appears to have been studied in cycloheptane derivatives, so we might be able to produce molecules with a variety of stereochemically defined functionalised substituents which could be employed in such studies. Thirdly, whilst cycloheptadiene and cycloheptadienyl complexes of iron (16), and other metals (17), are known, they have so far remained laboratory curiosities.

In terms of reactivity, tricarbonylcycloheptadienyliron tetrafluoroborate **43**, which is readily prepared either by hydride abstraction from the cycloheptadiene complex or by

protonation of the cycloheptatriene complex, is quite different from the cyclohexadienyl- $\text{Fe}(\text{CO})_3$ complex 24. Thus, reaction of 43 with nucleophiles can take three possible courses to give products of type 44, 45 and 46, depending on the nature of the nucleophile and reaction conditions (Scheme 12). Invariably, a mixture of products is obtained, giving individual complexes in low yield.

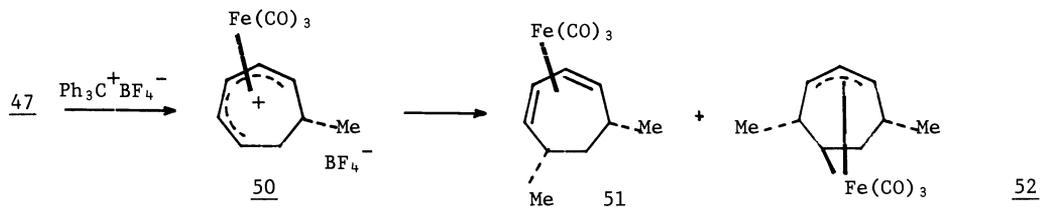


As an illustration of comparative reactivity of 24 and 43, results of reaction with lithium dimethyl cuprate and dimethyl sodiomalonate, obtained in our laboratory, are shown in Scheme 13. It can be seen that yields are lower with complex 43, particularly from the methylation reaction. In general, reactions of 43 with nucleophiles are not so clean, requiring extensive chromatographic purification of products.



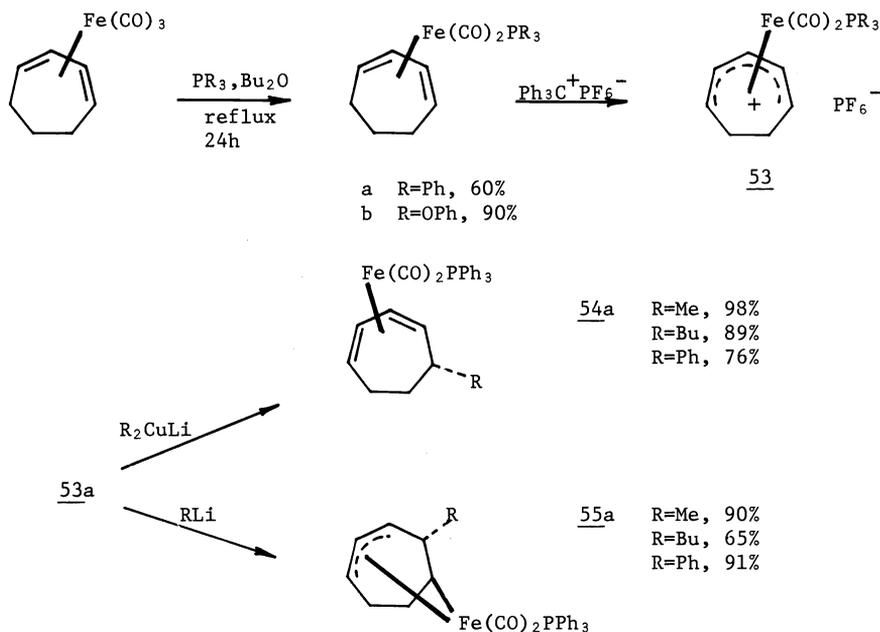
Despite the low yield of 47, we were able to use this compound to demonstrate that a second hydride abstraction could be accomplished in high yield, giving the dienyl complex 50. We were now in a position to assess whether a second nucleophile could be added to 50. Treatment with lithium dimethylcuprate afforded an inseparable 3:1 mixture of the dimethylated complexes 51 and 52, but in only 15-20% yield, the remaining material being accounted for by dimeric complexes and decomposition products (see later). On the other hand, reaction of 50 with methyl lithium resulted in no addition at C-1, the predominant pathway being C-2

addition to give 52 in 20% yield, together with dimeric species. These results are summarised in Scheme 14.

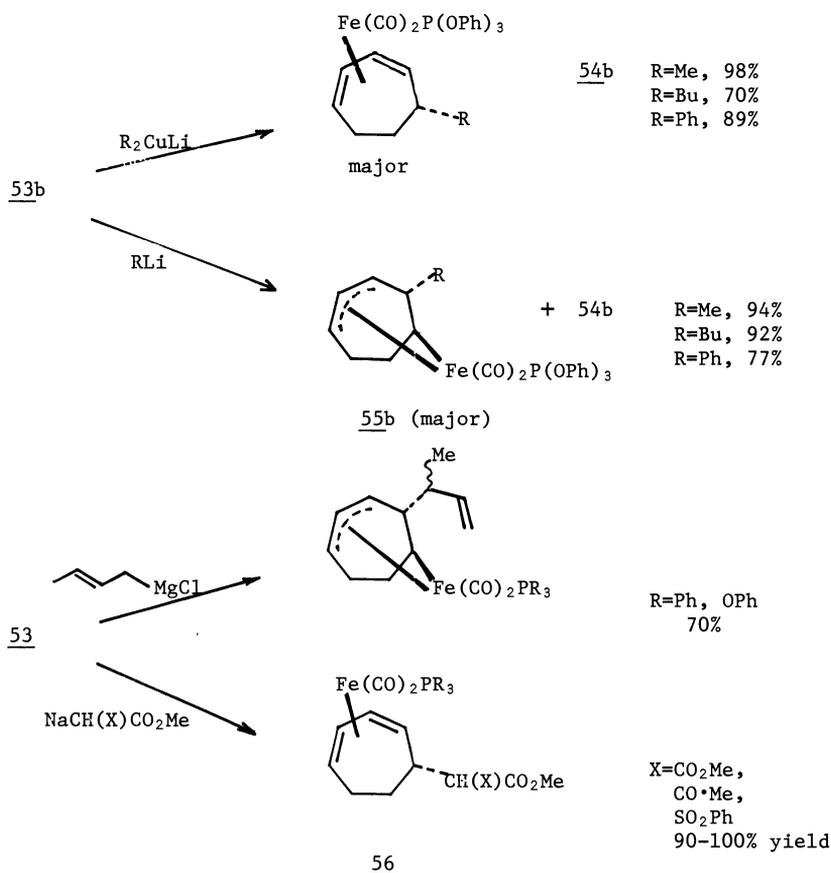


SCHEME 14

The results of Scheme 14 do establish the feasibility of attaining stereocontrolled functionalisation of cycloheptadiene, but the low yields prompted us to examine modification of the complex. During the methylation reactions we consistently observed the formation of considerable amounts of polar material (t.l.c.) which was unstable, but probably arises from nucleophile attack at carbonyl ligands. We argued that this mode of addition, as well as the reductive coupling to give dimers, might be overcome by increasing the electron density at the metal, for example, by replacing one CO ligand with a poorer π -acceptor, e.g., phosphine and phosphite derivatives 53a and 53b. Some very interesting results emerge from the study and these, together with the preparation of complexes, are shown in Schemes 15. It can be seen that considerable improvement in the methylation reactions is obtained, since reaction of 53a with lithium dimethylcuprate gives solely the product 54a of C-1 alkylation in virtually quantitative yield, whilst methyl lithium gives only C-2 alkylation, again in very high yield. Whilst 53b gives the C-1 methylation product 54b in essentially quantitative yield on treatment with lithium dimethylcuprate, a mixture of 54b and 55b, the latter being preponderant, is obtained from reaction with methyl lithium. Similar results are obtained with a range of organolithium and organocuprate reagents. We have also cursorily examined the reactions of allyl-Grignard and -cadmium reagents with these diene complexes, and found that these behave in analogous fashion to the lithium reagents.

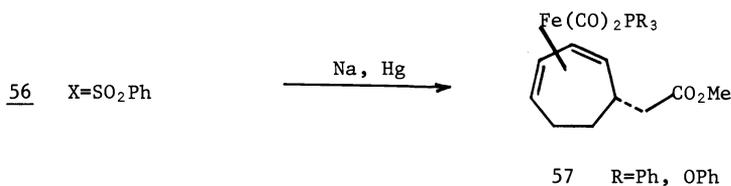


SCHEME 15 (continued overpage)



SCHEME 15

The triphenylphosphine and triphenylphosphite-substituted complexes also react satisfactorily with stable enolates. For example, reaction of $\underline{53a}$ or $\underline{53b}$ with dimethyl sodiomalonate leads to a single product $\underline{56}$ in essentially quantitative yield. Similar results are obtained with the corresponding acetoacetate and phenylsulfonylacetate enolates. The products from the latter reaction ($\underline{56}$, X = SO₂Ph) are useful in that they can be desulfurised to give monoester $\underline{57}$, though the yields are rather low (40-50%).



The methyl-substituted complexes $\underline{54}$ (a and b, R = Me) undergo regiospecific hydride abstraction to give quantitative yields of dienyl salts $\underline{58}$, and these undergo reactions similar to the unsubstituted derivatives, as shown in Scheme 16. That the second nucleophilic addition takes place stereospecifically is attested to by the fact that the dimethyl-substituted complex $\underline{59}$ is obtained as a single compound which shows only one doublet (6H, J = 6.5 Hz) at δ 0.79, corresponding to the two methyl groups, in the 200 MHz proton n.m.r. spectrum. The addition of nucleophiles *exo* to the metal is assumed by comparison with the cyclohexadienyl-Fe(CO)₃ systems (1), which we have never observed to undergo direct *endo* addition of nucleophiles.

We are currently studying a range of lactonisation reactions of 64 and 66, the initial results of which are interesting and highly encouraging. Details of the outcome of these reactions will be given elsewhere.

In conclusion, it can be seen that the use of organoiron methodology has considerable potential for the preparation of stereochemically defined cycloheptadienes which are expected to provide useful substrates for elaboration to natural products and for the study of conformation/reactivity interrelationships.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge the considerable efforts of my co-workers, some of whose names appear in the references. The successful developments at Case Western Reserve University, concerning the C-nor-D-homosteroid approaches, the diene lactonisation reactions and the studies on cycloheptadienyl-Fe(CO)₂L, are due to the efforts of Gi Rin Han, Tapan Ray, Sandra Kole and (in part) Bruce Chen. Our work in England was supported financially by the SERC, I.C.I., Pharmaceuticals and Plant Protection Divisions, and Beecham Pharmaceuticals, and our work in the U.S. is currently supported by N.I.H. (GM-30373-01 and GM-30757-01A1).

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