Pure & Appl. Chem., Vol. 66, No. 7, pp. 1415–1422, 1994.
Printed in Great Britain.

Tricarbonyliron lactone complexes in organic synthesis

Steven V. Ley

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK.

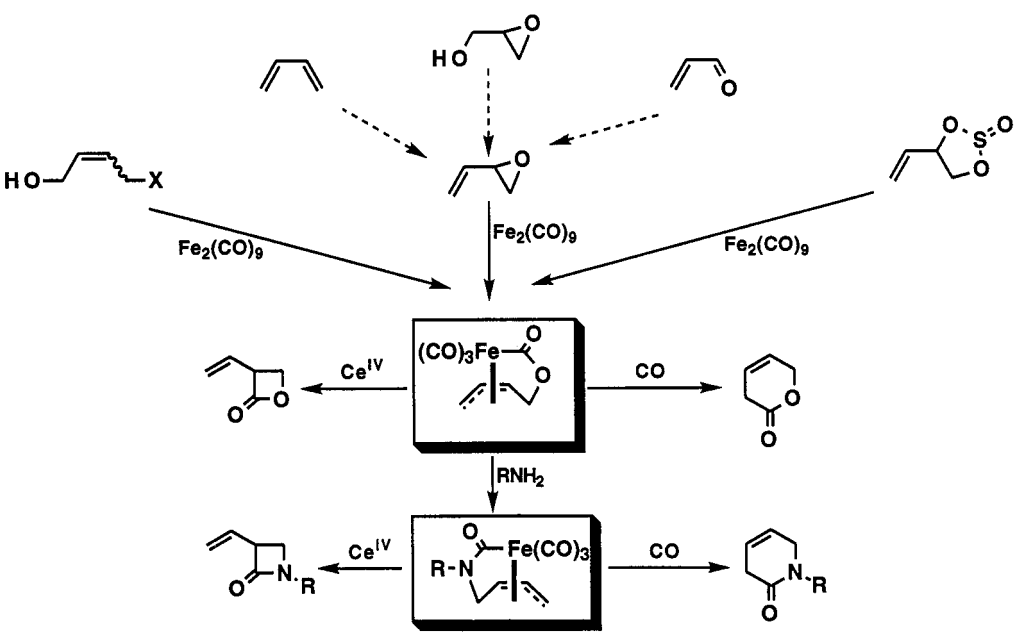
Abstract

The use of π-allyltricarbonyliron lactone and lactam complexes for the synthesis of lactones and lactams is described together with their application to the preparation of various biologically active molecules.

The use of organometallic species in organic synthesis often gives strategic advantages over conventional methods by promoting unique transformations. Consequently in recent years there have been tremendous advances in the utilisation of these species in the pharmaceutical and agrochemical industries.

For a number of years we have been interested in the use of π-allyltricarbonyliron lactone and lactam complexes in the synthesis of organic compounds (ref. 1). These complexes can be obtained from a wide range of precursors. Extrusion of the templating iron unit allows for the regioselective formation of lactones and lactams (Scheme 1) through a novel process in which the last bond forming step is ring closure.

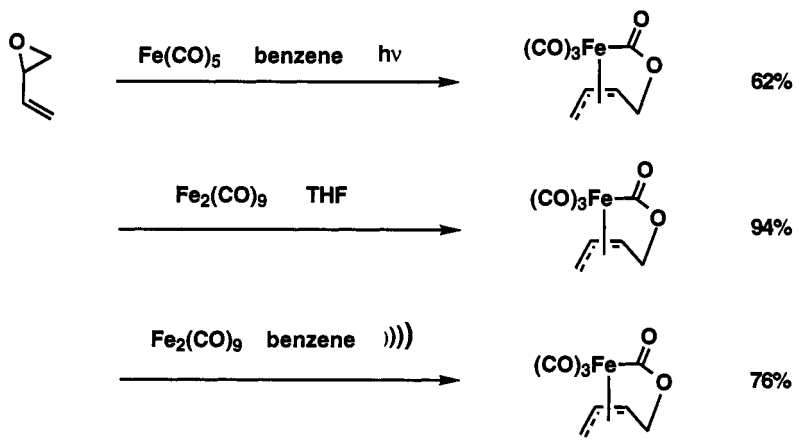
Scheme 1 ***π-Allyltricarbonyliron Lactone Complexes***



π-Allyltricarbonyliron lactone complexes were first prepared in very modest yields by Heck (ref. 2) and Murdoch (ref. 3) from butenediol derivatives using $Fe(CO)_5$ and $Fe_2(CO)_9$. The use of vinyl epoxides and $Fe(CO)_5$ under photolysis conditions, as introduced by Aumann (ref. 4) and Moriarty (ref. 5), resulted in considerably improved yields. The corresponding π-allyltricarbonyl iron lactam complexes could be obtained from oxazines (ref. 6), alkenyl aziridines (ref. 4) and by treatment of π-allyltricarbonyliron lactone complexes with amines in the presence of Al_2O_3 (ref. 6) or $AlCl_3$ (ref. 7). However, in order for these iron complexes to be useful in organic synthesis improved methods of preparation were required together with an understanding of their functional group compatibility and their reactivity towards a variety of reagents.

We have extended and improved the ways by which these complexes can be synthesised. In general the original photochemical route using $Fe(CO)_5$ as a source of co-ordinatively unsaturated iron carbonyl species and alkenyl epoxides works well. However, the volatility and toxicity of $Fe(CO)_5$, in combination with the high dilution necessary for photochemical reactions precludes this as the method of choice for the large scale (≥ 20g) preparation of these complexes. For these reasons we devised alternative, more convenient procedures which employ $Fe_2(CO)_9$, a crystalline material, as the reactive iron source. Dissolution of $Fe_2(CO)_9$ in THF is known (ref. 8) to produce a reactive chelated species $Fe(CO)_4$.THF which we reasoned would react with alkenyl epoxides to afford π-allyltricarbonyl lactone complexes. This turned out to be the case and gave excellent yields of product (ref. 9) and is now the method of choice for the preparation of these complexes. An alternative similarly efficient route has been devised (ref. 9) in which alkenyl epoxides react with $Fe_2(CO)_9$ in inert solvents such as benzene, toluene and hexane (which do not dissolve $Fe_2(CO)_9$) by the simple expedient of using ultrasound (ref. 10) to facilitate reaction. A comparison of the methods available to form these complexes is given below. (Scheme 2).

Scheme 2



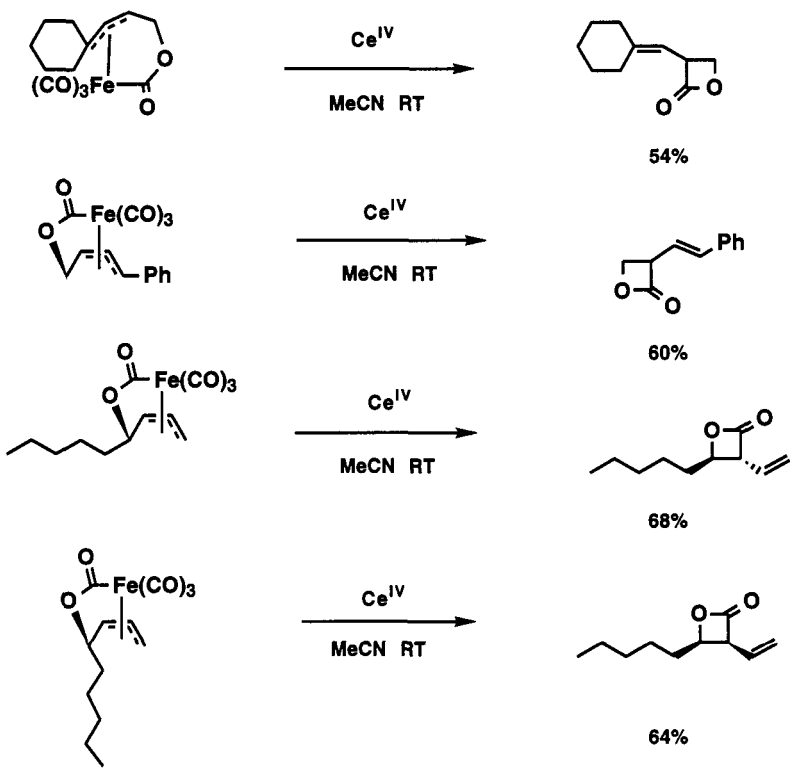
Owing to the volatility of alkenyl epoxides other potential precursors of π-allyltricarbonyliron lactone complexes have been investigated. Unsaturated diols which are, in some cases, easier to prepare than alkenyl epoxides and much less volatile seemed ideal candidates. They do indeed form iron complexes upon treatment with $Fe_2(CO)_9$ and we have studied this area extensively (ref. 11). It is worth noting that using our best conditions *cis*-but-2-ene-1,4 diol afforded a tricarbonyl complex in 73% yield which compares very favourably with the original Murdoch procedure which gives the same complex in 5% yield. Furthermore, we have noticed in some cases that the conditions used affect the product formed, with the desired tricarbonyliron complex being favoured by the ultrasonic conditions.

1,2-Diols also serve as precursors for iron complex formation *via* intermediate cyclic sulfites. This is particularly attractive as, like alkenyl epoxides, 1,2-diols can be prepared in enantiomerically pure form (ref. 12). The sulfites are readily prepared by treatment of the vicinal diols with thionyl chloride (ref. 13) and do not need to be oxidised further to the corresponding sulfates as they behave like alkenyl epoxides on reaction with $Fe_2(CO)_9$ (ref. 14).

Before discussing how these iron complexes may be used it is pertinent to comment on their physical and chemical robustness. They are reasonably stable materials that are often crystalline and can be subjected to chromatography on silica gel, alumina, or Florisil without decomposition. They remain intact during an increasingly large range of synthetic transformations such as oxidation with PCC, PDC, O_3, ^tBuOOH, MnO_2, $FeCl_3$, Et_3NO, and reduction with SmI_2 or hydrogen using a palladium supported on carbon catalyst. Similarly, they are unaffected by water, isonitriles, Lewis acidic organometallics, Et_3N, TMS-CN and Wittig reagents. Strongly basic or acidic conditions cause decomposition of these complexes as does exposure to vigorous reducing agents such as $NaBH_4$ and $LiAlH_4$. They are also unstable to temperatures above about 60 °C whereupon decarbonylation (ref. 4), decarboxylation, and rearrangement (ref. 15) occur to afford products which, occasionally, may be use of organic synthesis.

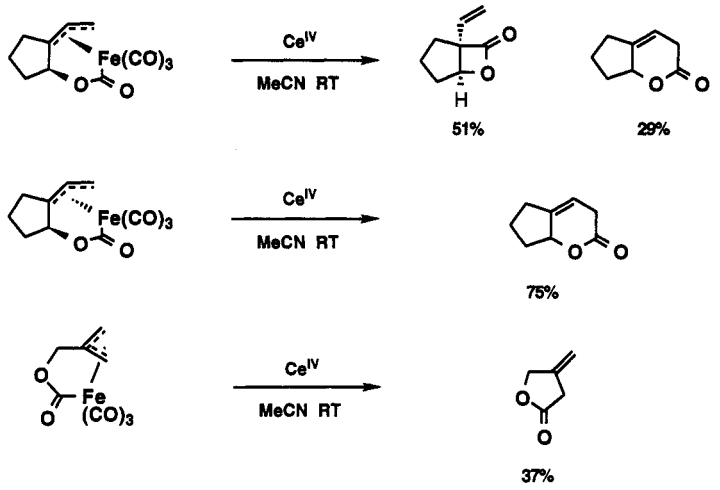
As to the use of these complexes in synthesis, our early experiments indicated that they could be readily converted to β-lactones upon decomplexation with ceric ammonium nitrate [CAN] (Scheme 3) (ref. 16). The predominance of β lactones does not occur in cases where the structure of the complex precludes the formation of 4-membered ring systems. Thus, the *anti*-tricarbonyliron complex (scheme 4) afforded exclusively the δ lactone upon treatment with CAN whilst the *syn*-tricarbonyliron complex gave the β-lactone as the major product. The examples in Scheme 4 also illustrate that 5-ring lactones are available by the appropiate choice of the iron complex.

Scheme 3 **β Lactone Synthesis**



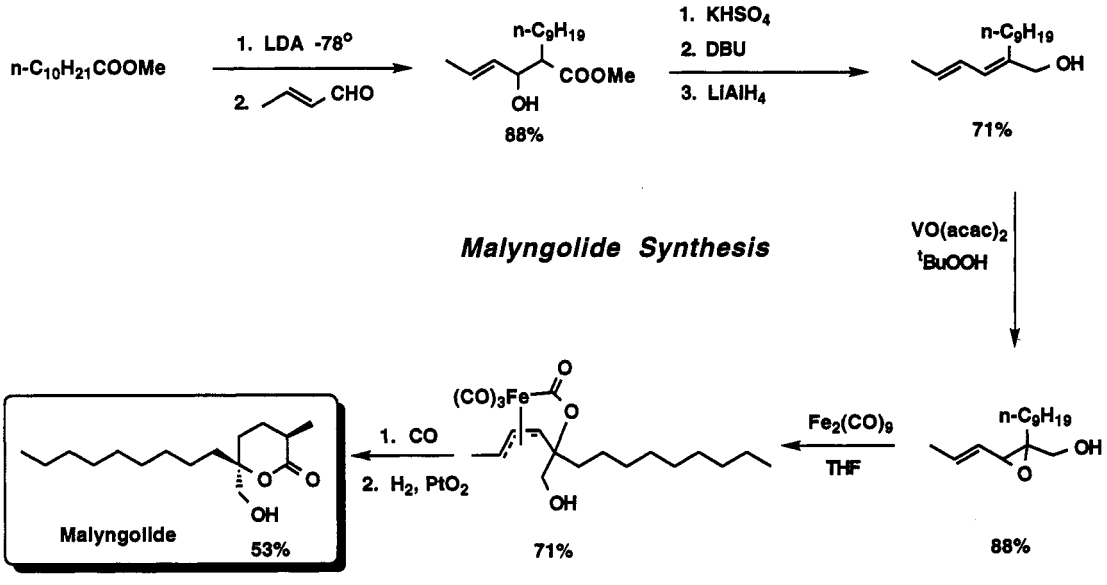
The most important aspect of this chemistry is that the stereochemistry of the complex controls the product stereochemistry. This, in combination with the preference for forming β-lactones makes the CAN decomplexation reaction a powerful tool in the synthesis of these ring systems. Since there is an increasing number of biologically active β-lactams being discovered it was attractive to exploit our novel method for their synthesis. Consequently we have used this chemistry in the total synthesis of several naturally occurring β-lactones including the pancreatic lipase inhibitor Valilactone (ref. 17).

Scheme 4 ***Lactone Synthesis***



We next turned out attention to the use of these complexes for the synthesis of biologically active δ-lactones and have presently completed the preparation of five natural products (refs. 18, 19). One advantage of this methodology is illustrated by the synthesis of the antibiotic Malyngolide (Scheme 5). More conventional means of forming lactones would require protection of the primary hydroxyl group, whilst here it can be carried through the various transformations unprotected without causing interference. We have also used these methods to prepare key intermediates during the total syntheses of other important natural products such as the ionophore antibiotic routiennocin (ref. 20) and the potent antiparasitic agent avermectin B1a (ref. 21). For the selective conversion of π-allyltricarbonyliron lactone complexes to unsaturated δ-lactones we used the conditions originally developed by Aumann (ref. 7) which employs exhaustive carbonylation with CO at 60 atmospheres and a temperature of 130 °C. We now prefer to use a higher pressure of CO, upto 300 atmospheres, and a lower temperature, around 90 °C.

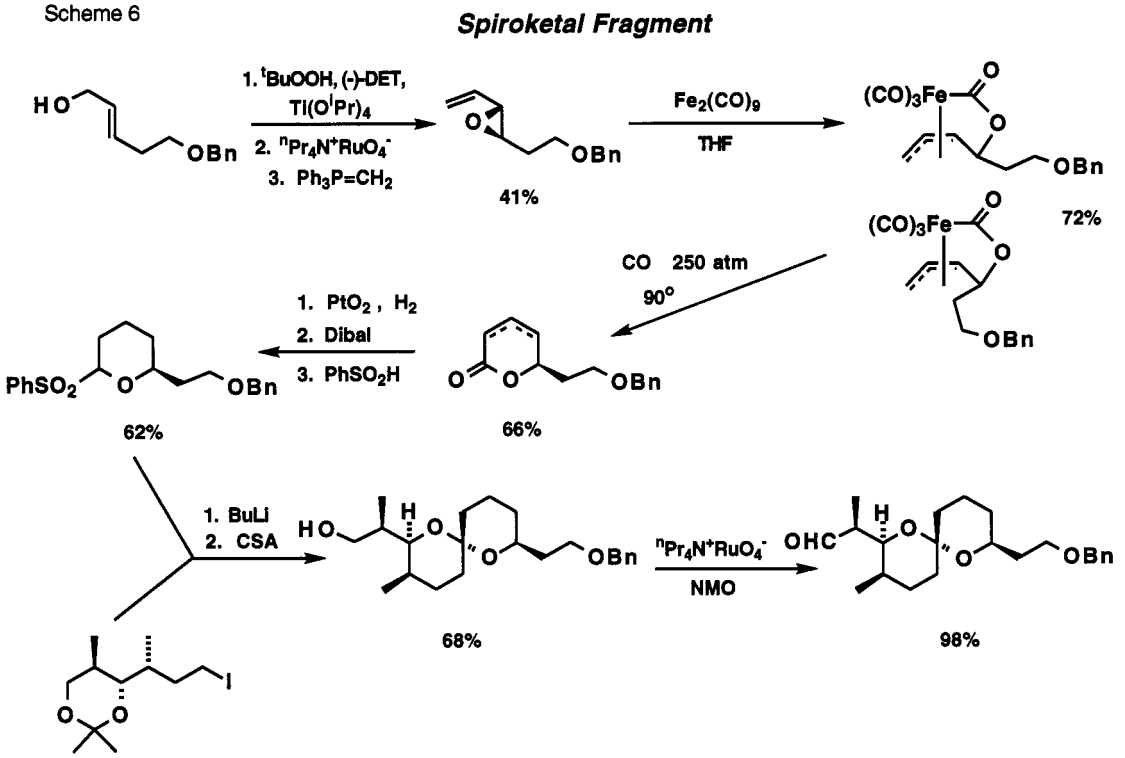
Scheme 5



Routiennocin is a spiroketal ionophore antibiotic very similar in structure to the related calcium binding agent calcimycin. For its synthesis we considered a convergent approach which would bring together four components which were deliberately chosen to exploit much of the chemistry developed in our

laboratories. Since this synthesis has been published previously (ref. 20) there is no need to discuss in detail the preparation of all the various components, rather the use of the iron carbonyl chemistry will be emphasised (Scheme 6). In order to obtain the required chiral benzene sulfonyl tetrahydropyran fragment the π-allyltricarbonyl iron complexes were needed whereby the carbon bearing the allyl and iron lactone oxygen atom was of the correct absolute configuration for the natural product. This was achieved using the Sharpless epoxidation procedure (ref. 22) to set-up the desired chirality. Following oxidation with tetra-n-propylammonium perruthanate, TPAP, a catalytic room temperature oxidant which we developed (ref. 23), Wittig coupling gave the alkenyl epoxide precursor. Treatment with $Fe_2(CO)_9$ in THF then afforded the iron carbonyl complexes. These were subjected to carbonylation at 90°C and 250 atmospheres to provide the lactones which were converted to the sulfone following previously established procedures (ref. 24). The sulfone was subsequently coupled *via* its anion with the chiral iodide to give the spiroketal after a cascade of designed reactions operating in one pot. Further oxidation with TPAP afforded an aldehyde which was condensed with 2-lithio-SEM-pyrrole (ref. 25) and oxidised once again with TPAP to give the pyrrole carbonyl derivative which was subsequently transformed to the natural product (Scheme 7). In another natural product synthesis we have exploited the use of π-allyltricarbonyliron lactone complexes for the construction of both the bis-oleandrose carbohydrate component and the spiroketal unit of the antiparasitic macrolide avermectin B1a (ref. 26). These more complex natural product syntheses serve to illustrate the power of the iron carbonyl methodology in the preparation of functionally elaborated δ-lactones.

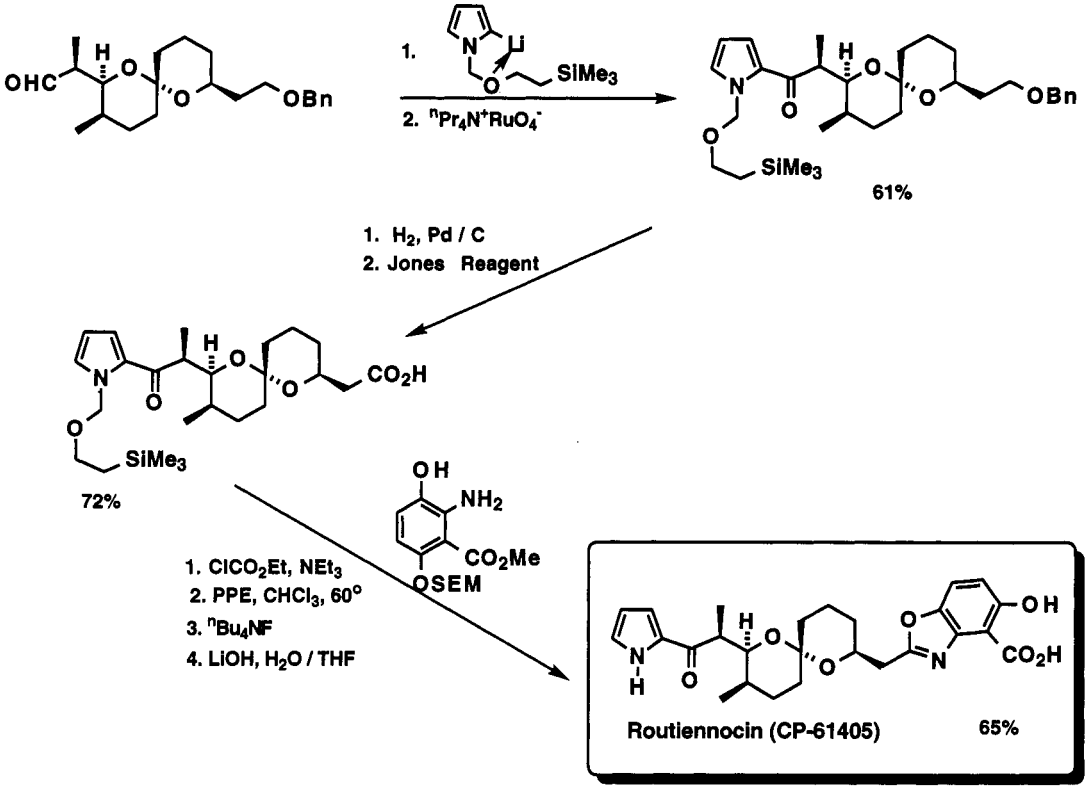
Scheme 6



Following the success of the method for the formation of β-lactones from π-allyltricarbonyliron complexes it was tempting to apply similar methods for β-lactam synthesis from the corresponding tricarbonyliron lactam complexes (ref. 27). This is especially attractive since the β-lactam ring occurs in many important pharmaceutical compounds such as the carbapenems, thienamycin, the monobactams and the nocardicin antibiotics. As a prelude to the more complex examples we found that simple tricarbonyliron lactone complexes underwent S_N2' like reaction (ref. 7) with amines in the presence of Lewis acids, especially $ZnCl_2$, to give the corresponding iron-lactam complexes. These undergo oxidation with ceric ammonium nitrate to produce β-lactams selectively and in high yield. We have used these methods to achieve formal syntheses of the nocardicins (ref. 28) and thienamycin. (ref. 29). As an alternative to this method of preparation of iron-lactam complexes we have also developed a route *via* intermediate cyclic sulphamidites. In Scheme 8 we illustrate the use of this process for the synthesis of some pyrrolizidine alkaloids (ref. 30).

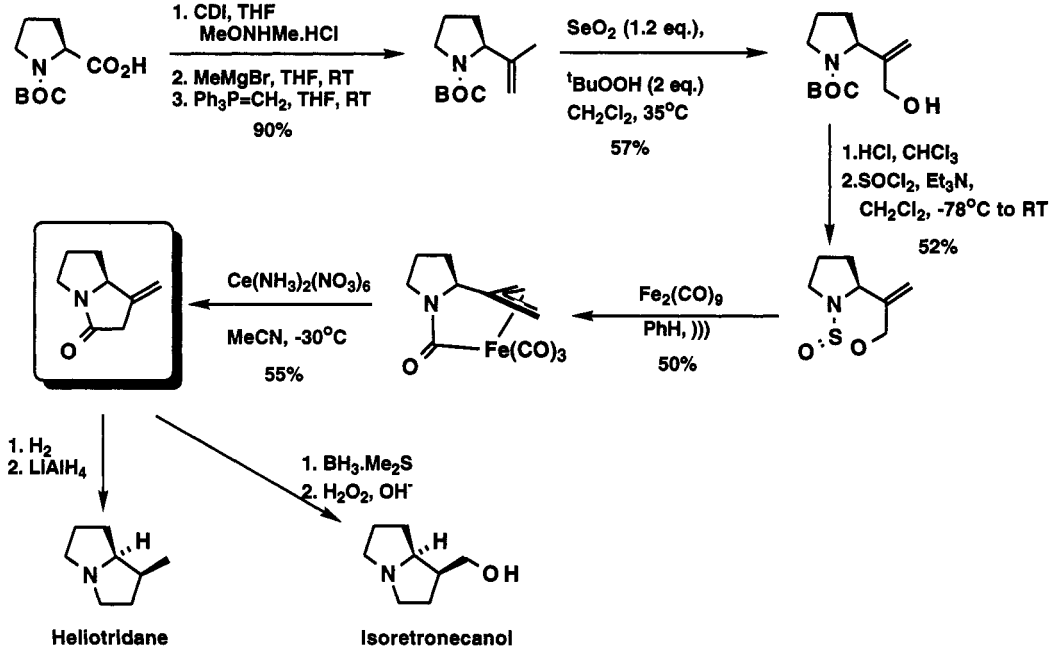
Scheme 7

Final Steps



Scheme 8

Pyrrolizidine Alkaloid Synthesis



In all of the above examples we have used the iron carbonyl group as a temporary tether and source of carbon monoxide for subsequent reactions. We now propose to use these compounds as templates for asymmetric reactions. The inherent chirality associated with the irontricarbonyl unit is ideally placed to allow highly stereoselective addition reactions to substituents located in close proximity to it. These reactions would open up new possibilities for asymmetric synthesis, with the potential to control the formation of several stereogenic centres and provide novel ways of controlling remote stereocentres. Furthermore, these complexes could be rearranged using $Ba(OH)_2$ (ref. 4) to give enantiomerically pure η^4 diene-irontricarbonyl complexes which would be useful for further synthetic transformations.

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