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Organic synthesis with tricarbonyliron lactone complexes

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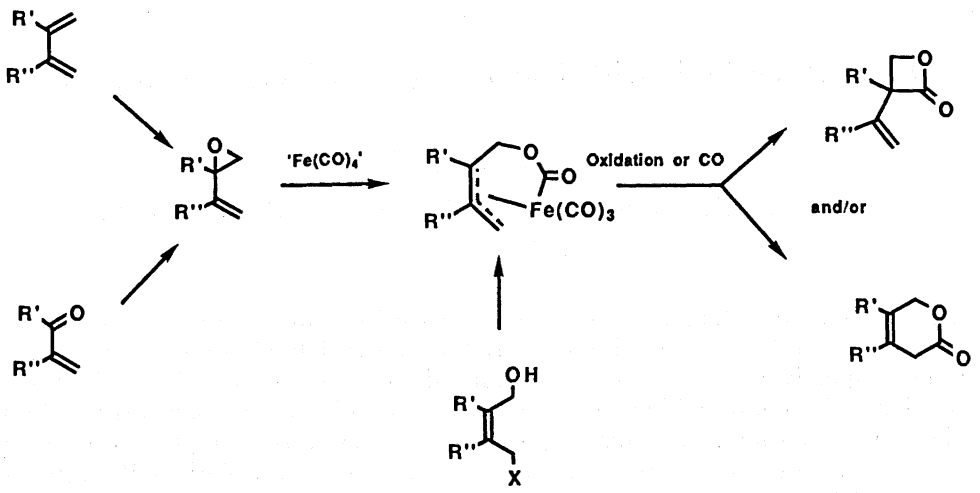
π-Allytricarbonyliron lactone complexes are useful precursors for organic synthesis. These stable complexes are readily prepared from a variety of organic substrates and may be respectively converted to β- and δ-lactones by selective oxidation or exhaustive carbonylation. The natural products massoialactone, parasorbic acid, the carpenter bee pheromone and malyngolide were prepared by using the iron carbonyl methodology, along with precursors for the ionophore antibiotic CP 61405 and avermectin B1a synthesis. Several corresponding lactam complexes were obtained by treatment of the π-allytricarbonyliron lactones with amines in the presence of Lewis acids. These complexes were used in the formal total synthesis of the nocardicins and (+)-thienamycin.

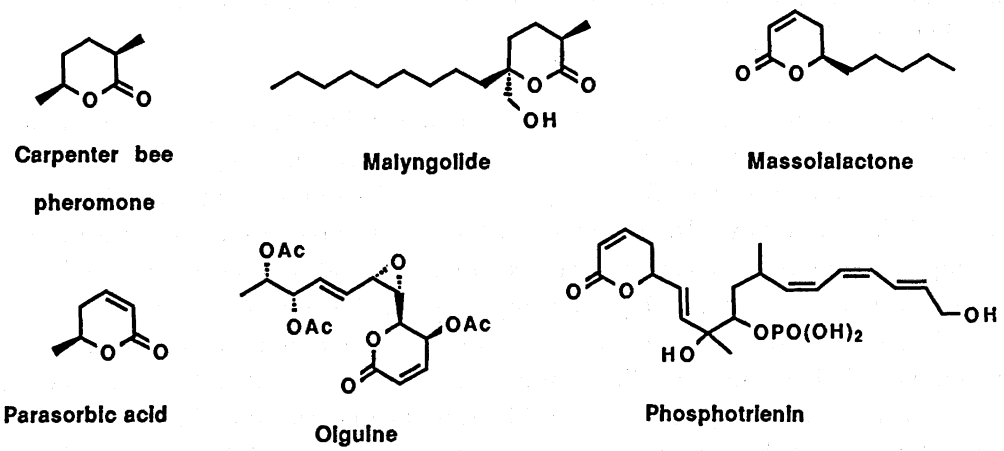
π-Allyltricarbonyliron lactone complexes have been known since 1964 and have been obtained from a variety organic precursors (Heck & Boss 1964; Murdoch 1964; Aumann *et al.* 1974; Chen *et al.* 1975). For example, they may be prepared from alkenyl epoxides or various butendiols and their derivatives by treatment with iron carbonyls. Improvements in the yields of these complexes may be achieved under especially mild conditions using ultrasonic methods or by the use of solutions of $Fe_2(CO)_9$ in tetrahydrofuran (Horton *et al.* 1984). We find these methods to be superior to the original conditions in which either $Fe(CO)_5/h\nu$ or $Fe_2(CO)_9$/heat were employed. These new conditions use the more easily handled di-iron nonacarbonyl, show wider substrate tolerance, and avoid problems that can occur at higher temperature such as decarbonylation, decarboxylation or metal-catalysed hydrogen shifts (Annis *et al.* 1982).

We reasoned that these air-stable, chromatographable and often crystalline π-allyltricarbonyliron complexes, might be interesting and novel starting materials for organic synthesis (Ley *et al.* 1984). In particular we speculated that these complexes could, upon oxidation or carbonylation lead to unsaturated lactonic materials depending upon which bonds became coupled (scheme 1). The method would also be readily applicable to natural-product synthesis. For example, one might envisage routes to both saturated and unsaturated δ-lactones such as those shown in scheme 2. Also, by appropriate modification, routes to several biologically interesting β-lactones would be possible (scheme 3).

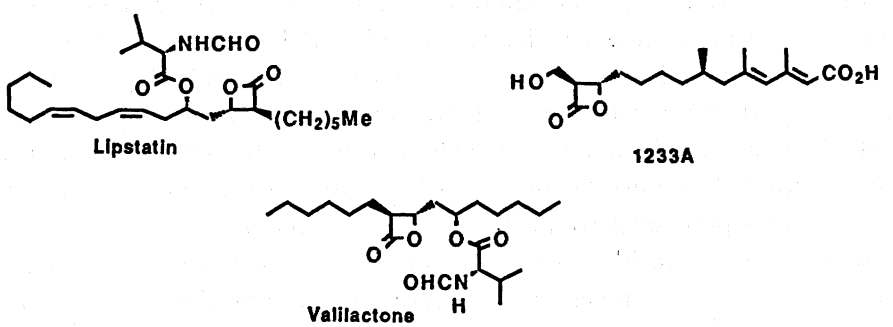
In order to test the above ideas several simple ferrilactones were prepared via alkenyl epoxides and their subsequent reactions with ceric ammonium nitrate or carbon monoxide were studied. Our initial results, several years ago, showed the viability of the process (Annis & Ley 1977; Annis *et al.* 1981). For example, a vinyl cyclopentyl epoxide reacted with $Fe(CO)_5$ to give two iron complexes designated as *syn*- or *anti*-depending on the relative position of the tricarbonyliron group with respect to the bridging oxygen atom. Interestingly, upon oxidation these complexes afforded different product ratios, which reflected the initial stereoselectivity. The *syn*-complex gave a β-lactone as the major product whereas the *anti*-complex gave the β,γ-unsaturated δ-lactone (scheme 4) (Annis *et al.* 1979).



Scheme 1

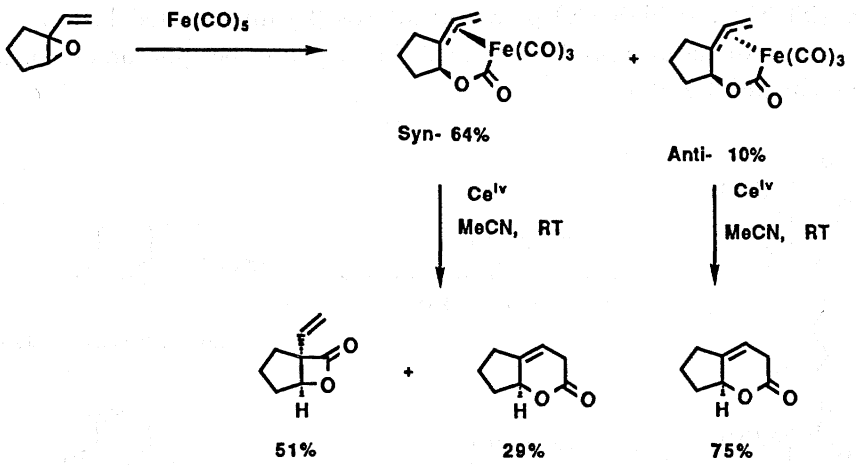


Scheme 2

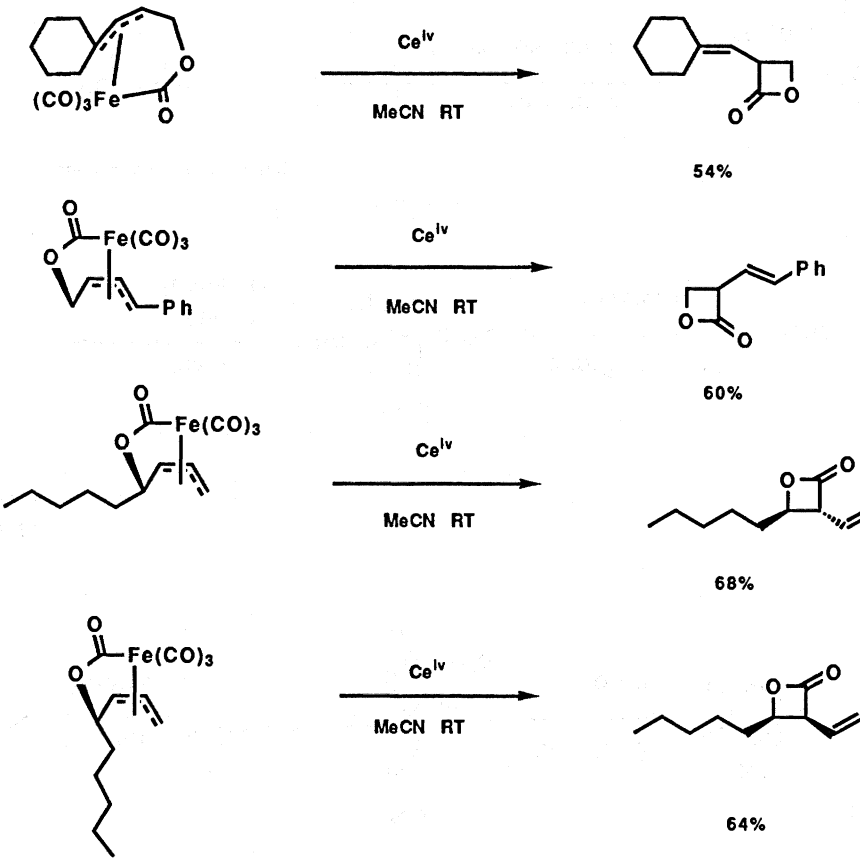


Scheme 3

However, in most other examples (scheme 5) the β-lactone was the major product. This method therefore constitutes a novel route to β-lactones that we hope may be applicable to more challenging targets molecules such as the potent inhibitor of pancreatic lipase, lipstatin (Weibel *et al.* 1987), the inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) synthase, antibiotic 1233A (Omura *et al.* 1987), or the cellular membrane esterase inhibitor,



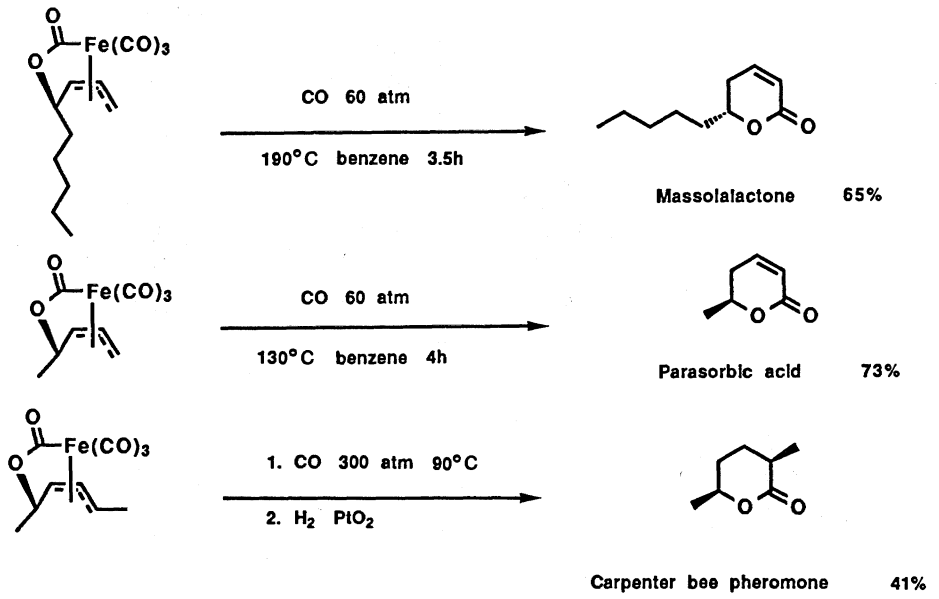
SCHEME 4



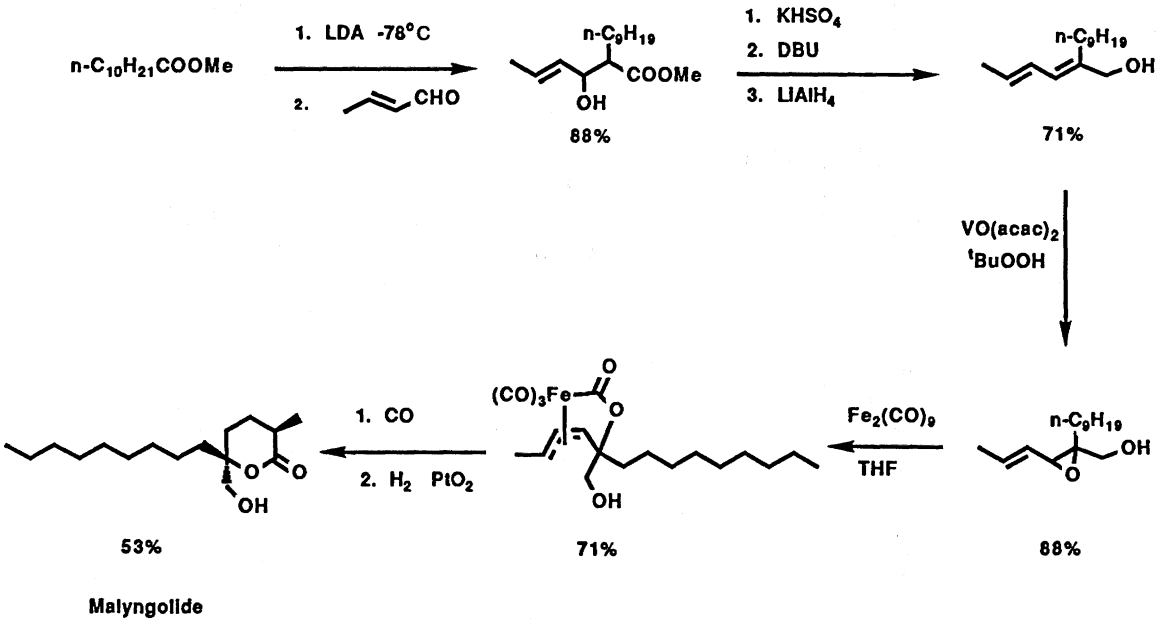
SCHEME 5

valilactone (Kilahara 1987). The use of π-allyllactone complexes as precursors for δ-lactone synthesis has also been demonstrated (Annis *et al.* 1982; Aumann *et al.* 1979). Indeed, this provides a rapid entry to α,β-unsaturated lactone natural products: massoialactone and parasorbic acid are obtained upon exhaustive carbonylation of appropriate precursors at high temperature (scheme 6) (Horton & Ley 1985). Alternatively carbonylation at lower

temperatures (90 °C) and high CO pressures affords β,γ-unsaturated lactones, which upon hydrogenation provide natural products such as the carpenter bee pheromone or the antibiotic malyngolide (schemes 6 and 7).

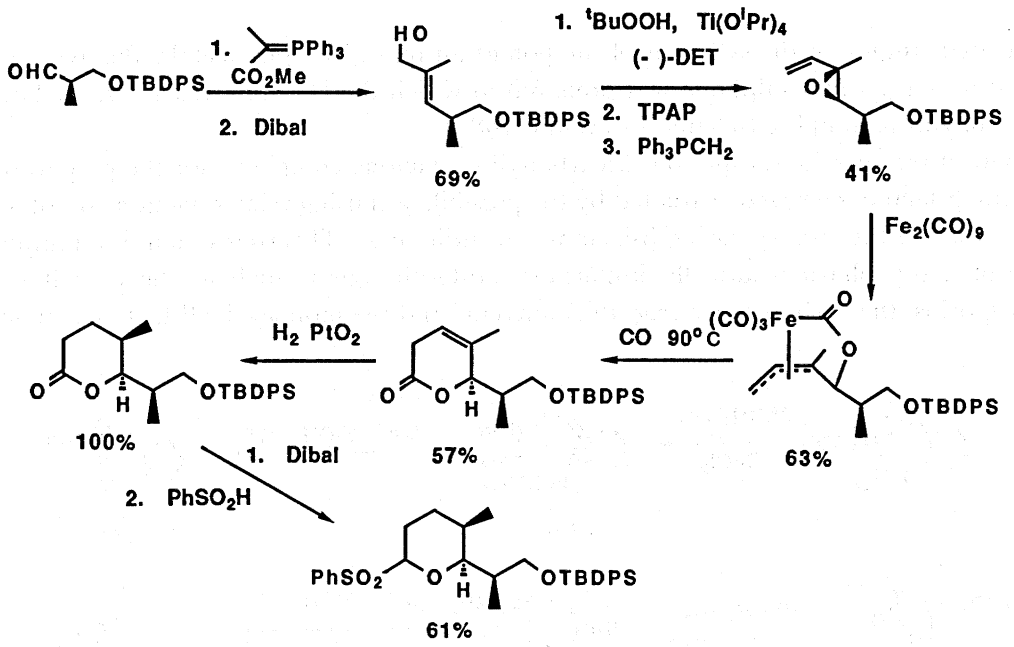


Scheme 6

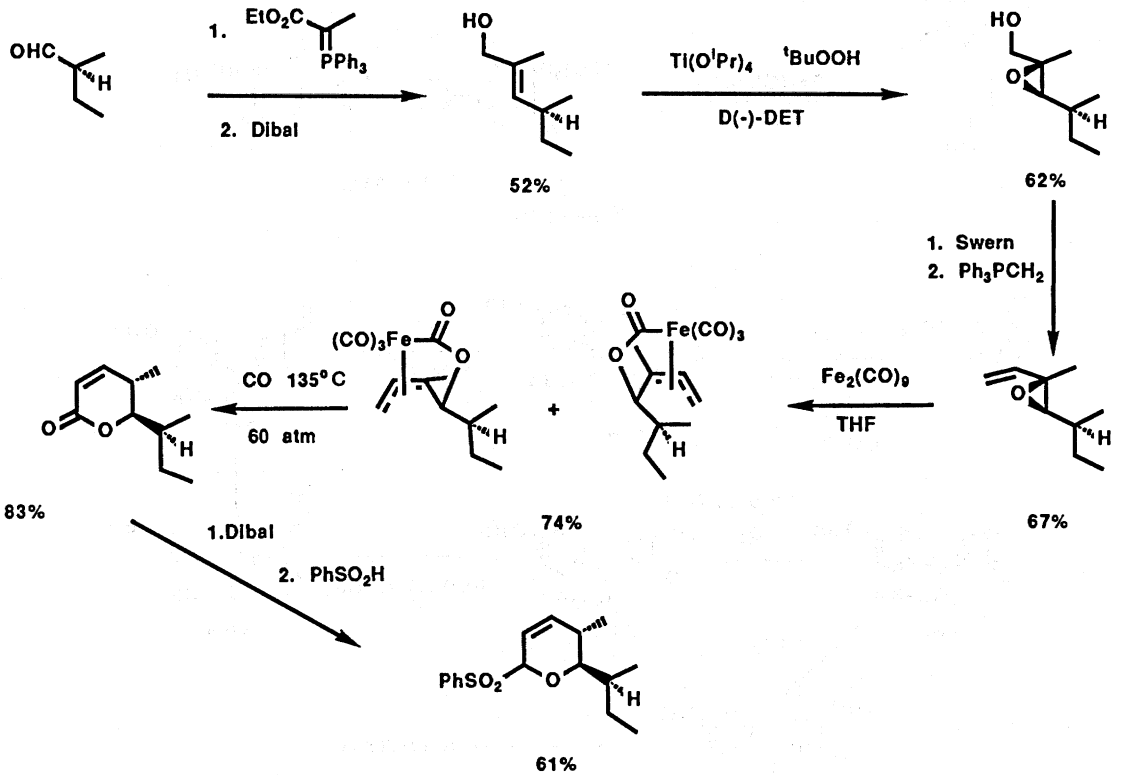


Scheme 7

During our work on the synthesis of the ionophore antibiotic CP 61405 we have also exploited the iron carbonyl complex methodology for the preparation of key structural fragments. In this way a tetrahydropyranyl sulphone was obtained (scheme 8) that will eventually be coupled, based upon our previous studies (Ley *et al.* 1986) with related



SCHEME 8

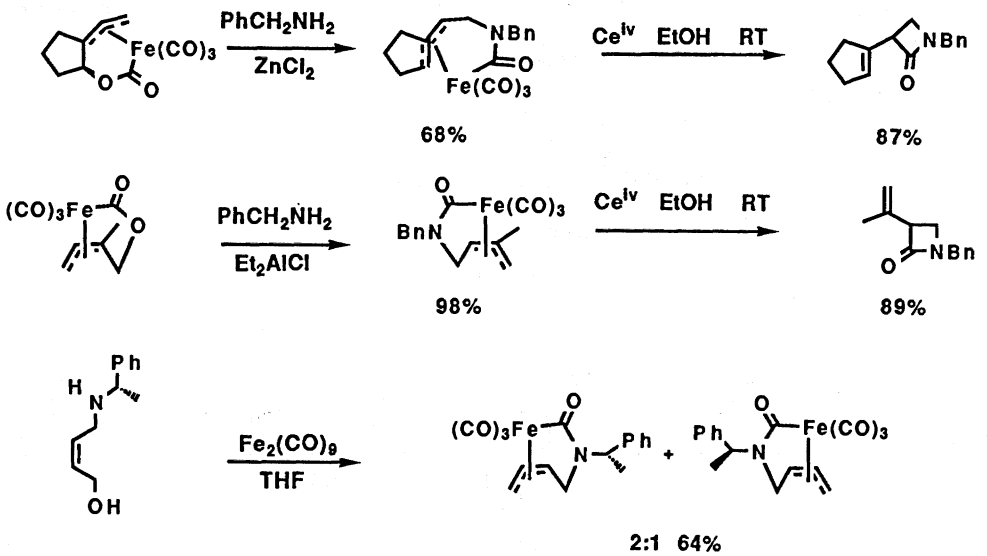


SCHEME 9

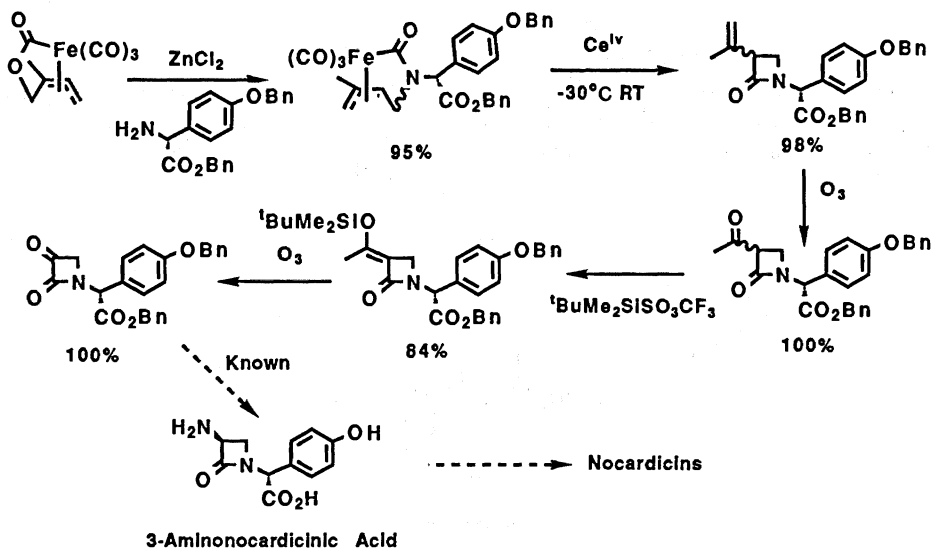
sulphones, to afford the central spiroacetal fragment of CP 61405 (Organ 1987; White 1988).

In related studies on the synthesis of the potent antiparasitic spiroacetals, the avermectins, an unsaturated pyranyl sulphone was prepared in which the key step was a carbonylation of a tricarbonyliron complex (scheme 9) (White 1988).

In view of the success in using the tricarbonyliron lactone complexes for the preparation of small-ring β-lactones we were attracted by the possibility of using related lactam complexes for the formation of the corresponding β-lactams (azetidinones). This ring system is an important feature of many pharmaceutically important antibiotic agents such as the penicillins, the cephalosporins, the carbapenems (e.g. thienamycin) and the monocyclic β-lactam systems the



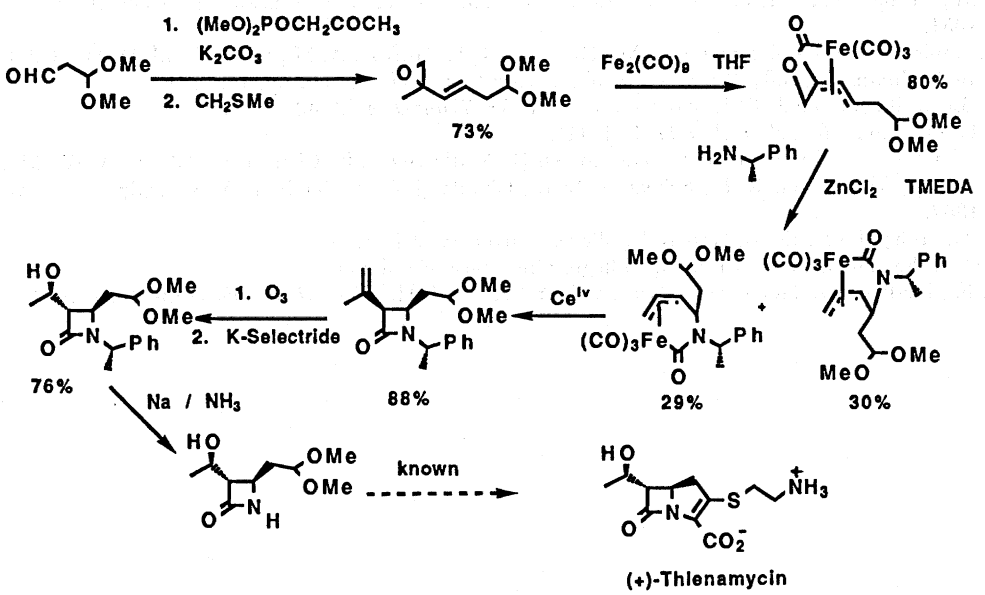
Scheme 10



Scheme 11

nocardicins and monobactams. The required tricarbonyliron lactam complexes may be obtained from the ferrilactones by treatment with amines in the presence of Lewis acids such as $ZnCl_2$/TMEDA or from butenolamines with $Fe_2(CO)_9$ (scheme 10).

Others have reported the use of 1,2-oxazines as precursors for lactams (Becker *et al.* 1974, 1976). The ferrilactams, which are formed from the iron lactones by an S_N2' reaction, may be oxidized with ceric ammonium nitrate to give β-lactams, generally in excellent yield (Annis *et al.* 1983). The method has been applied to the synthesis of (−)-3-oxo-1-[(*p*-benzyloxyphenyl)-benzyloxycarbonylmethyl] azetidin-2-one, which is a known building block for the preparation of the monocyclic nocardicins (scheme 11) (Hodgson *et al.* 1985*a*). We have also used related chemistry for the formal total synthesis of the carbapenem antibiotic (+)-thienamycin (scheme 12) (Hodgson *et al.* 1985*b*).



SCHEME 12

The use of tricarbonyliron lactone and lactam complexes for the preparation of lactones and lactams has been demonstrated. However, there is considerable scope for future developments, particularly in the exploitation of the asymmetric aspects of the reaction, and for the systematic study of the effects of functional group substitution.

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REFERENCES

Annis, G. D., Hebblethwaite, E. M., Hodgson, S. T., Hollinshead, D. M. & Ley, S. V. 1983 *J. chem. Soc. Perkin Trans.* I, pp. 2851–2856.

Annis, G. D. & Ley, S. V. 1977 *J. chem. Soc. chem. Commun.*, pp. 581–582.

Annis, G. D., Ley, S. V., Self, C. R. & Sivaramakrishnan, R. 1981 *J. chem. Soc. Perkin Trans.* I, pp. 270–277.

Annis, G. D., Ley, S. V., Self, C. R., Sivaramakrishnan, R. & Williams, D. J. 1982 *J. chem. Soc. Perkin Trans.* I, pp. 1355–1361.
Annis, G. D., Ley, S. V., Sivaramakrishnan, R. Atkinson, A. M., Rogers, D. M. & Williams, D. J. 1979 *J. organometall. Chem.* **182**, C11–C14.
Aumann, R., Frohlich, K. & Ring, H. 1974 *Angew. Chem.* **13**, 275–276.
Aumann, R., Ring, H., Kruger, C. & Goddard, R. 1979 *Chem. Ber.* **112**, 3644–3671.
Becker, Y., Eisenstadt, A. & Shvo, Y. 1974 *Tetrahedron* **30**, 839–847.
Becker, Y., Eisentadt, A. & Shvo, Y. 1976 *Tetrahedron* **32**, 2123–2126.
Chen, K.-N., Moriarty, R. M., De Boer, B. G., Churchill, M. R. & Yeh, H. J. S. 1975 *J. Am. chem. Soc.* **97**, 5602–5603.
Heck, R. F. & Boss, C. R. 1964 *J. Am. chem. Soc.* **86**, 2580–2583.
Hodgson, S. T., Hollinshead, D. M., Ley, S. V. 1985*a* *Tetrahedron* **41**, 5871–5878.
Hodgson, S. T., Hollinshead, D. M., Ley, S. V., Low, C. M. R. & Williams, D. J. 1985*b* *J. chem. Soc. Perkin Trans.* I, pp. 2375–2381.
Horton, A. M., Hollinshead, D. M. & Ley, S. V. 1984 *Tetrahedron* **40**, 1737–1742.
Horton, A. M. & Ley, S. V. 1985 *J. organometall. Chem.* **285**, C17–C20.
Kilahara, M., Hsano, M., Naganawa, H., Maeda, M., Hoyagi, T. & Umezawa, H. 1987 *J. Antibiotics* **40**, 1647–1651.
Ley, S. V., Annis, G. D., Hebblethwaite, E. M., Hodgson, S. T., Horton, A. M., Hollinshead, D. M., Self, C. R. & Sivaramakrishnan, R. 1984 *Royal Society of Chemistry Spec. Publ.* No. 50, pp. 148–161.
Ley, S. V., Lygo, B., Sternfeld, F. & Wonnacott, A. 1986 *Tetrahedron* **42**, 4333–4342.
Murdoch, H. D. 1964 *Helv. chim. Acta* **47**, 936–941.
Omura, S., Tomoda, H., Kumagai, H., Greenspan, M. D., Yodkovitz, J. B., Chen, J. S., Alberts, A. W., Martin, I., Mochales, S., Monaghan, R. L., Schwartz, R. E., Chabla, J. C. & Patchett, A. A. 1987 *J. Antibiotics* **40**, 1356–1357.
Organ, H. M. 1987 Ph.D. thesis, Imperial College, University of London.
White, A. D. 1988 Ph.D. thesis, Imperial College, University of London.
Weibel, E. K., Hadvary, P. Hochuli, E., Kuper, E. & Lengsfeld, H. 1987 *J. Antibiotics* **40**, 1081–1091.

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