π-Allyltricarbonyliron Lactone Complexes in Synthesis: Application to the Synthesis of the β-Lactam Antibiotic (+)-Thienamycin

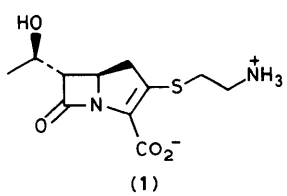
Simon T. Hodgson, David M. Hollinshead, and Steven V. Ley*

Department of Chemistry, Imperial College, London SW7 2AY, U.K.

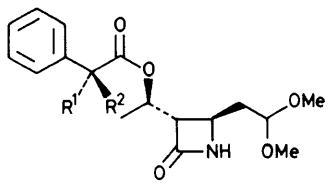
Synthesis of an enantiomerically pure β-lactam intermediate used in the preparation of the antibiotic (+)-thienamycin is described, by suitable elaboration of a functionalised π-allyltricarbonyliron complex.

π-Allyltricarbonyliron lactone complexes are useful precursors for the preparation of simple lactones[1] and lactams.[2] Here we show that the method is also applicable to a more challenging problem involving the synthesis of the important β-lactam antibiotic (+)-thienamycin (**1**).[3]

The enone (**2**)† [readily available in 84% yield from 3,3-dimethoxypropanal and dimethyl (2-oxopropyl)phosphonate] gave the alkenyl epoxide (**3**) (89%) upon treatment with dimethylsulphonium methylide in dimethyl sulphoxide–tetrahydrofuran (DMSO–THF). Reaction of (**3**) with pentacarbonyliron, [$Fe(CO)_5$], and ultraviolet irradiation provided the stable, crystalline π-allyltricarbonyliron lactone complex (**4**) in 90% yield. Alternatively, a more convenient procedure involved reaction of the epoxide with nonacarbonyl di-iron, [$Fe_2(CO)_9$], in THF solution at room temperature[4] to give (**4**) in 84% yield. The *syn,anti* configuration of (**4**) was assigned on the basis of the observed 3,4-*trans* coupling constant of 12 Hz and by analogy with previous studies.[2] Insertion of (−)-(1*S*)-α-methylbenzylamine into the complex (**4**) mediated by $ZnCl_2$·TMEDA (TMEDA=tetramethylethylenediamine),[2] proceeded slowly (7 h) to give the diastereoisomeric lactam complexes (**5**) and (**6**) in 29 and 30% yields respectively arising from attack by the amine in an S_N' like reaction. This reaction was also accompanied by a small amount (16%) of the tricarbonyliron diene complex (**7**). The diastereoisomeric ferrilactam complexes were readily separated by chromatography and their absolute configurations determined on the basis of subsequent transformations. Oxidation of the tricarbonyliron lactam complex (**5**) with cerium(IV) ammonium nitrate in methanol at −30 °C, gave the *cis*-β-lactam (**8**) in excellent yield (87%) (Scheme 1). The *cis*-arrangement of the 3,4-substituents was apparent from its high field ^1H n.m.r. spectrum which showed a large $J_{3,4}$ coupling constant of 6 Hz in agreement with other examples.[5] Low temperature (−78 °C) ozonolysis of (**8**) proceeded smoothly to give the corresponding 3-acetyl derivative, which isomerised completely on silica gel chromatography to the more stable *trans*-isomer (**9**). Stereoselective reduction of (**9**) was achieved using K-Selectride–KI–diethyl ether at 0 °C to give the (1′*R*)-hydroxyethylazetidinone (**10**) with its (1′*S*)-epimer in the ratio 9 : 1, in agreement with selectivity observed in similar systems.[6] Reductive removal of the *N*-α-methylbenzyl group was effected using sodium in liquid ammonia to provide the optically pure hydroxyethyl β-lactam (**11**) in 75% yield, $[\alpha]_D^{22}$ + 11.4° (*c* 1.3 in $CHCl_3$) (Scheme 1). Thus the chiral benzyl group has served both as a handle to facilitate diastereoisomer separation of (**5**) and (**6**) and a protecting group for the azetidinone nitrogen.



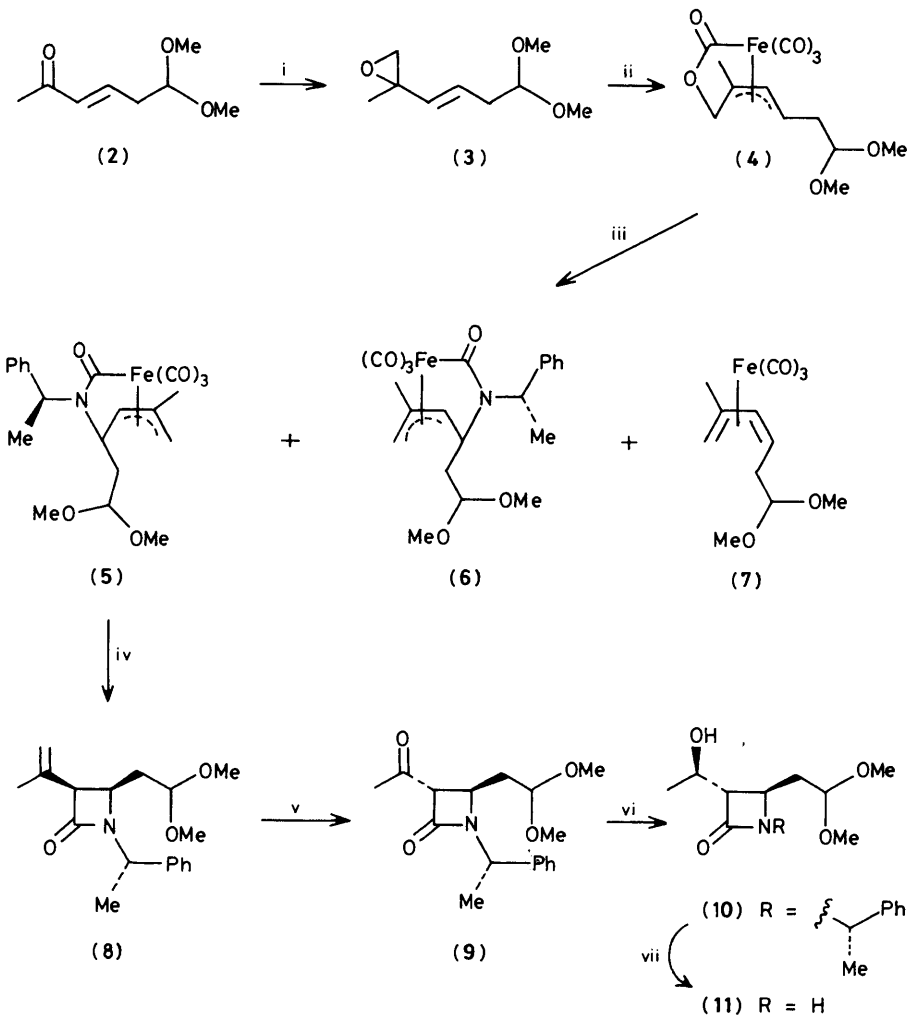
(1)



(12) $R^2 = CF_3$, R^1 = OMe

(13) R^2 = OMe, $R^1 = CF_3$

† All new compounds are fully characterised by spectroscopic and microanalytical methods.



Scheme 1. i, $Me_2S{=}CH_2$, DMSO–THF, 0 °C; ii, $Fe(CO)_5$ (4.5 equiv.), *hν*, benzene or $Fe_2(CO)_9$ (1.5 equiv.), THF; iii, (−)-(1*S*)-α-methylbenzylamine (3 equiv.), $ZnCl_2$·TMEDA (2 equiv.), THF–Et_2O, 7 h; iv, $(NH_4)_2Ce(NO_3)_6$, MeOH, −30 °C →room temp.; v, O_3, CH_2Cl_2, −78 °C, work-up with Me_2S and silica gel chromatography; vi, KI (1.2 equiv.), K-Selectride (2.5 equiv.) in diethyl ether–THF 7:1, 0 °C; vii, Na, NH_3, EtOH, −77 °C.

Table 1. ^{1}H N.m.r. chemical shifts (δ) for the (*R*)-(+)- and (*S*)-(−)-MTPA esters of compound (**11**).

	2′-Me	3-H	$MeOCCF_3$	4-H	$CH(OMe)_2$	CHOR
(**12**)	1.41	3.03	3.51	3.66	4.39	5.45
(**13**)	1.50	2.98	3.54	3.52	4.31	5.45

The absolute configuration of (**11**) was determined by conversion into its diastereoisomeric (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)-α-phenylacetyl (MTPA) esters (**12**) and (**13**) according to Mosher's n.m.r. configuration–correlation method.[7] Mosher's model predicts that diastereoisomer (**12**) from (*R*)-(+)-MTPA, will exhibit an upfield shift for the C-2′ methyl resonance and a corresponding downfield shift for the 3-H, 4-H, and CF_3 resonances relative to its counterpart (**13**) derived from (*S*)-(−)-MTPA, if the side chain has the (*R*)-configuration. Indeed examination of the high field ^{1}H n.m.r. spectra of (**12**) and (**13**) shows this to be the case (Table 1). Support for applying Mosher's model to β-lactams possessing the hydroxyethyl side chain at C-3 of an azetidinone nucleus follows from similar derivatisation experiments.[8‡]

Since (**11**) has been converted into thienamycin by an adaptation[9] of the Merck procedure the route described above constitutes a formal total synthesis of (**1**) in its enantiomerically pure natural form.

We thank the S.E.R.C. and Johnson Matthey p.l.c. for a C.A.S.E. award (to D. M. H.), Imperial College External Development Fund (grant to S. T. H.), Beecham Pharmaceuticals (Brockham Park) for generous financial assistance,

‡ A report by Kametani *et al.*[10] describes an asymmetric synthesis of thienamycin in which the undesired un-natural enantiomer of (**11**) predominated in poor (16—20%) enantiomeric excess. Similar derivatisation of this mixture with (*S*)-(−)-MTPA provided limited ^{1}H n.m.r. data for the minor isomer, agreeing closely with that of (**13**). The lactam complex (**6**) was also converted by a similar route into the antipodal derivative $[\alpha]_D^{22}$ −10.7° (*c* 0.8, $CHCl_3$), corresponding to (**11**) whose Mosher esters exhibited ^{1}H n.m.r. data again in accord with predictions.

and the Royal Society of Chemistry for the Hickinbottom Research Award (to S. V. L.).

Received, 26th January 1984; Com. 115

References

1 G. D. Annis, S. V. Ley, C. R. Self, and R. Sivaramakrishan, *J. Chem. Soc., Perkin Trans.* 1, 1981, 270; R. Aumann, H. Ring, C. Krüger, and R. Goddard, *Chem. Ber.*, 1979, **112**, 3644.

2 G. D. Annis, E. M. Hebblethwaite, and S. V. Ley, *J. Chem. Soc., Chem. Commun.*, 1980, 297; G. D. Annis, E. M. Hebblethwaite, S. T. Hodgson, D. M. Hollinshead, and S. V. Ley, *J. Chem. Soc., Perkin Trans.* 1, 1983, 2851.

3 For enantiospecific syntheses of (+)-thienamycin, see: T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, and F. A. Bouffard, *J. Am. Chem. Soc.*, 1980, **102**, 6161; S. Karady, J. S. Amato, R. A. Reamer, and L. M. Weinstock, *ibid.*, 1981, **103**, 6765; P. J. Reider and E. J. J. Grabowski, *Tetrahedron Lett.*, 1982, **23**, 2293; M. Miyashita, N. Chida, and Y. Yoshikohsi, *J. Chem. Soc., Chem. Commun.*, 1982, 1354; S. Hanessian, D. Desilets, G. Rancourt, and R. Fortin, *Can. J. Chem.*, 1982, **60**, 2292; N. Ikota, O. Yoshino, and K. Koga, *Chem. Pharm. Bull.*, 1982, **30**, 1929; M. Shiozaki, N. Ishida, H. Maruyama, and T. Hiraoka, *Tetrahedron*, 1983, **39**, 2399; K. Okano, T. Izawa, and M. Ohno, *Tetrahedron Lett.*, 1983, **24**, 217.

4 D. M. Hollinshead, A. M. Horton, and S. V. Ley, *Tetrahedron*, in the press.

5 D. M. Brunwin and G. Lowe, *J. Chem. Soc., Perkin Trans.* 1, 1973, 1321; F. DiNinno, T. R. Beattie, and B. G. Christensen, *J. Org. Chem.*, 1977, **42**, 2960.

6 F. A. Bouffard and B. G. Christensen, *J. Org. Chem.*, 1981, **46**, 2208; F. Pecquet and J. d'Angelo, *Tetrahedron Lett.*, 1982, **23**, 2777.

7 J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.

8 G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 6491.

9 T. Kametani, S.-P. Huang, T. Nagahara, S. Yokohama, and M. Ihara, *J. Chem. Soc., Perkin Trans.* 1, 1981, 964.

10 T. Kametani, T. Nagahara, and M. Ihara, *J. Chem. Soc., Perkin Trans.* 1, 1981, 3048.