Tetrahedron Vol 42, No. 18, pp. 5123 to 5137, 1986
Printed in Great Britain

0040-4020/86 $3.00 + .00

The Asymmetric Synthesis of β-Lactams. Stereocontrolled Asymmetric Tandem Michael Additions and Subsequent Alkylations of E-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH=CHMe]. X-Ray Crystal Structure of (RS)-E-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH=CHMe]

Stephen G. Davies,* Isabelle M. Dordor-Hedgecock,
Kevin H. Sutton and Jonathan C. Walker,

The Dyson Perrins Laboratory, South Parks Road, OXFORD, OX1 3QY, U.K.

and

Richard H. Jones and Keith Prout,

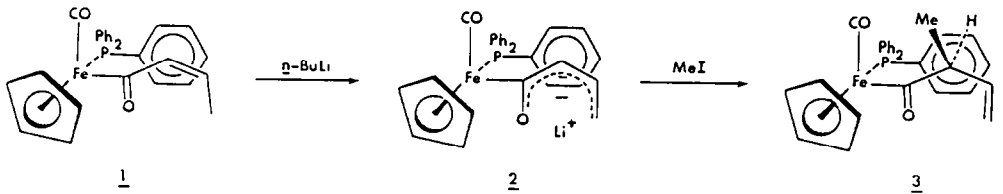
Chemical Crystallography Laboratory, 9, Parks Road, OXFORD, OX1 3PD, U.K.

(*Received in UK* 26 *June* 1986)

Summary: Michael addition of methyllithium to the E-crotonyl complex (RS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH=CHMe] followed by trapping of the resultant enolate with methyl iodide gives (RS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(Me)$CHMe_2$] (d.e. > 100:1), also generated by treatment of (RS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OMe)_2$] with three equivalents of methyllithium and methyl iodide. Addition of n-butyllithium to the (RS)-E-crotonyl complex followed by protonation with methanol occurs with high diastereoselectivity. Quenching with methyl iodide gives (RS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(Me)CH(Me)n-Bu], also generated by treating either diastereoisomer of [(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2$CH(Me)OMe] with two equivalents of n-butyllithium and methyl iodide. Decomplexation gives the known erythro-2,3-dimethylheptanoic acid. Similarly, Michael addition of lithium benzylamide and electrophilic quenching with methanol or methyl iodide occurs with high diastereoselectivity and gives upon decomplexation, 4-methyl- and cis-3,4-dimethyl-N-benzyl-β-lactams respectively. The stereochemical results are rationalised by addition occurring to the E-crotonyl complex in the anti (C=O to CO) and cisoid conformation and subsequent alkylation of the unhindered face of the E-enolate generated. Confirmation is provided by an X-ray crystal structure analysis of (RS)-E-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH=CHMe]. When repeated with the optically pure (S)-E-crotonyl complex, decomplexation gives essentially optically pure (2R),(3R)-(-)-N-benzyl-2,3-dimethylheptanamide, (4S)-(-)-4-methyl- and (3R),(4S)-(-)-cis-3,4-dimethyl-N-benzyl-β-lactams.

Introduction:

The chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)]† exerts powerful stereochemical control during the reactions of attached acyl ligands.[1,2] For example, the Z-crotonyl iron complex 1 is deprotonated in the cisoid conformation by n-butyllithium to the dienolate 2 which undergoes highly stereoselective α-methylation from the unhindered face generating 3 as a single diastereoisomer.[3,4].



1 2 3

We describe here in detail the highly stereoselective tandem Michael additions to and subsequent electrophilic quenching of the racemic E-crotonyl iron complex 4 which result in the stereocontrolled synthesis of α- and β-substituted iron acyl complexes. Part of this work has been

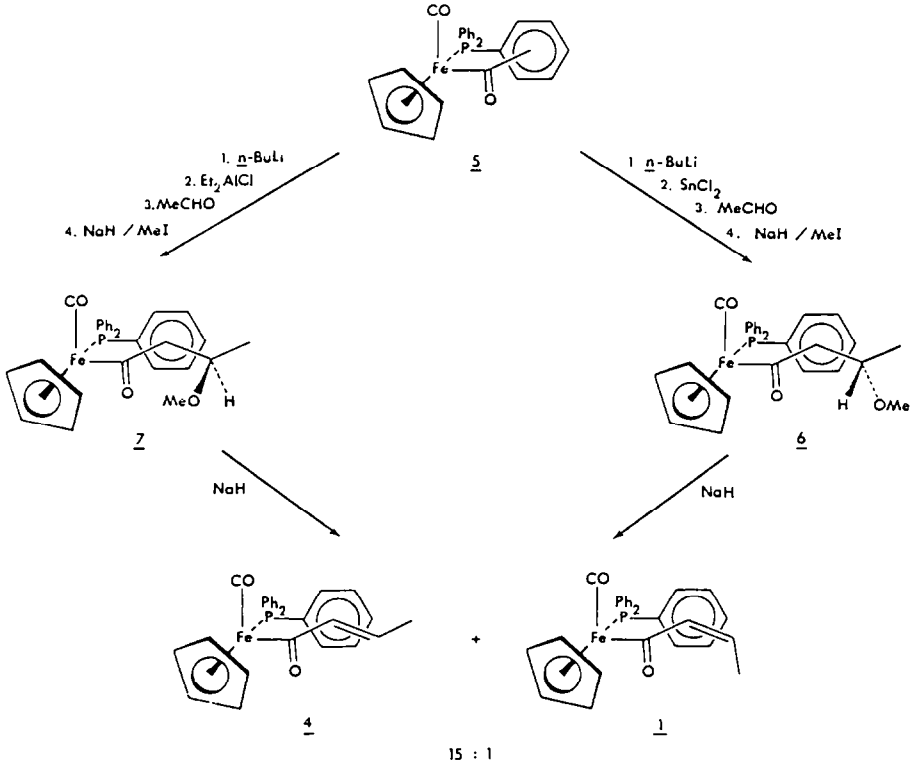
† Unless otherwise stated all complexes are racemic but only those with the R configuration at iron are drawn for clarity.

the subject of a preliminary communication[3] and similar reactivity was subsequently reported independently by Liebeskind *et.al.*[5] We then go on to report such tandem reactions of *n*-butyllithium and lithium benzylamide to the enantiomerically pure (S)-E-crotonyl complex 4 which upon decomplexation give essentially optically pure α,β-disubstituted carbonyl compounds and 4-mono- and 3,4-disubstituted β-lactams respectively, all of known absolute configuration.

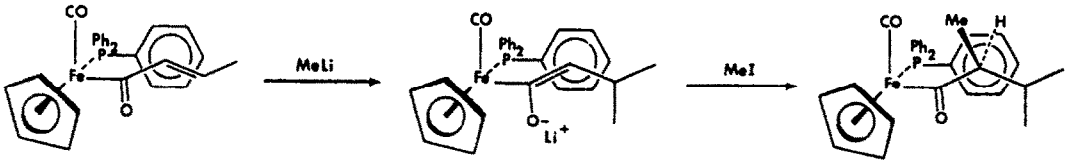
The possibility of the tandem stereocontrolled formation of two chiral centres *via* Michael additions of carbanions to α,β-unsaturated carbonyl compounds and subsequent alkylation of the enolate thus formed has been recognised for some time. In general the use of a chiral auxiliary as part of the α,β-unsaturated carbonyl equivalent has proved the more successful approach.[6,7,8] In particular, where part or all of the α,β-unsaturated carbonyl moiety is contained in a ring system, moderate to good stereocontrol can be achieved in the formation of both the α- and β-centres.[6,7] For the corresponding acyclic cases however, good stereocontrol has only been achieved in the initial Michael addition, *i.e.* at the β-centre.[6,8,9]

Results and Discussion:

Several methods for the synthesis of the E-crotonyl iron complex 4 have been described recently.[3,10,11] The most efficient synthesis involves the sodium hydride-promoted elimination of methoxide from the β-methoxy acyl complexes 6 and 7 which are derived from the parent acetyl complex 5 *via* aldol reactions with acetaldehyde and subsequent O-methylation.[10] This route generates a readily separable 15:1 mixture of the E- and Z-crotonyl complexes 4 and 1 respectively.

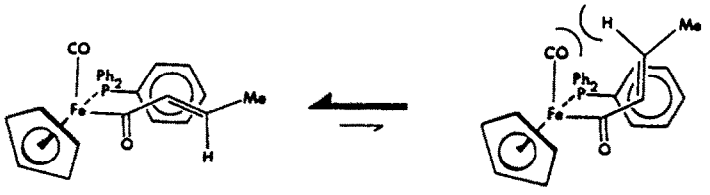


Addition of methyllithium followed by methyl iodide to the E-crotonyl iron complex 4 in THF at -78°C generated the α,β-dimethyl butanoyl complex 9 as a single diastereoisomer (d.e. >100:1 by 300 MHz ^{1}H n.m.r. spectroscopy). The relative configurations of the iron to the α-centre were established from the chemical shift (δ0.91) of the α-methyl doublet which is characteristic of the RS,SR-diastereoisomer.[12] The formation of 9 as the exclusive product indicates that 4 is undergoing a Michael addition with the methyllithium to generate an enolate which is then trapped by the methyl iodide. Since α-methylation must have occurred from the unhindered face[1], the intermediate enolate must have the E-configuration. This is consistent with 4 undergoing a Michael addition in the *cisoid* conformation thus generating E-enolate 8.



4 8 9

Assuming, in common with all other iron acyls of this type,[13] that the acyl oxygen remains anti to the CO ligand then molecular models and extended Huckel calculations[14] indicate a clear preference for 4 to adopt a cisoid conformation. Steric interactions between the β-hydrogen and the CO ligand would destabilise the corresponding transoid conformation.



CISOID 4 TRANSOID

These predictions were verified by an X-ray crystal structure analysis of 4 (Figure 1). Selected bond lengths and bond angles are given in Table 1 and final atomic coordinates are listed in Table 2. The geometry around the iron centre is close to octahedral and the acyl oxygen is anti to the CO ligand (Figure 2). The E-crotonyl conformation is cisoid with the torsional angle between the C=O and the C=C bonds being 39°. Figure 3 shows a projection down the Fe-P axis and illustrates the blocking effect of the triphenylphosphine ligand.

Table 1*

Selected bond lengths (Å), angles (°) and torsional angles (°) with e.s.d.s in parentheses for (RS)-E-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH=CHMe].

Fe(1)-P(1)	2.195(1)	Fe(1)-C(1)-C(2)	118.9(3)
Fe(1)-C(1)	1.958(3)	C(1)-C(2)-C(3)	121.7(4)
Fe(1)-C(5)	1.738(3)	C(2)-C(3)-C(4)	125.8(5)
C(1)-O(1)	1.223(4)	Fe(1)-P(1)-C(11)	116.1(1)
C(1)-C(2)	1.488(5)		
C(2)-C(3)	1.316(6)	C(5)-Fe(1)-C(1)-O(1)	-161
C(3)-C(4)	1.484(6)	C(1)-Fe(1)-P(1)-C(11)	-30
		C(1)-C(2)-C(3)-C(4)	171
C(1)-Fe(1)-C(5)	95.2(2)	C(5)-Fe(1)-C(1)-C(2)	18
C(1)-Fe(1)-P(1)	89.2(1)	C(3)-C(2)-C(1)-O(1)	39
P(1)-Fe(1)-C(5)	91.8(1)	Fe(1)-P(1)-C(11)-C(16)	-66
Fe(1)-C(1)-O(1)	122.9(3)		

* The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW (Great Britain). Any request should be accompanied by the full literature citation for this paper.

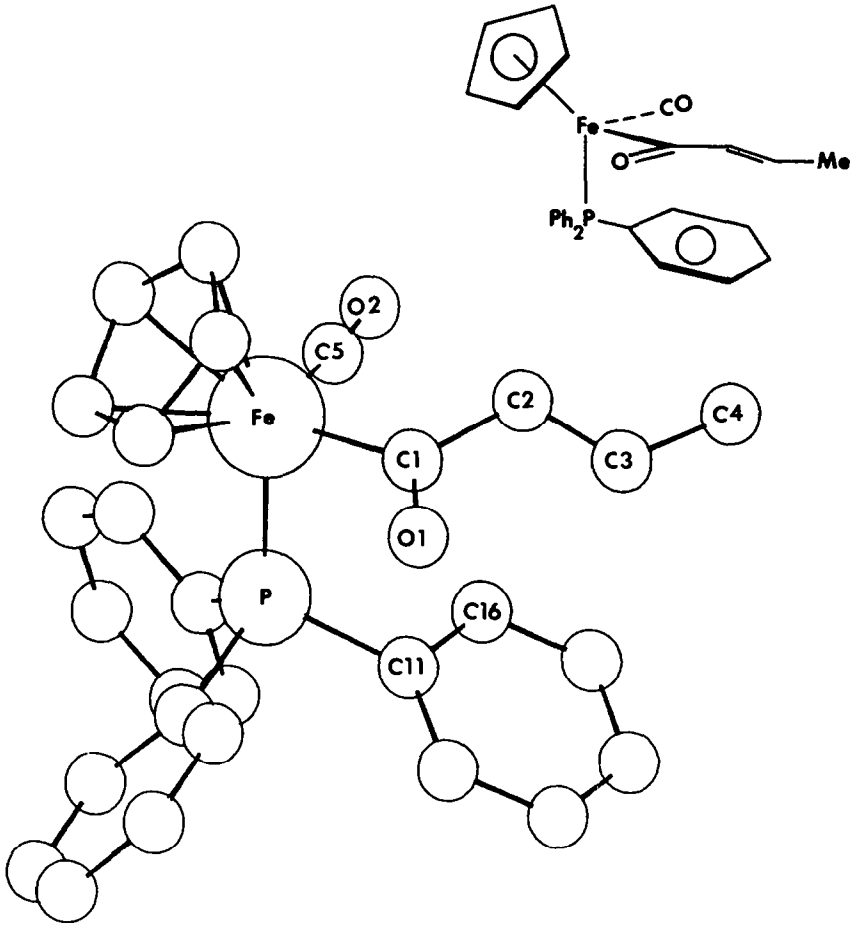


Figure 1.

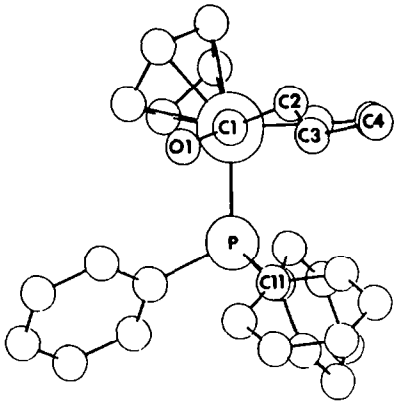


Figure 2.

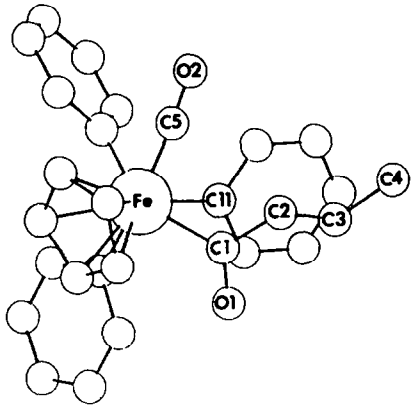


Figure 3.

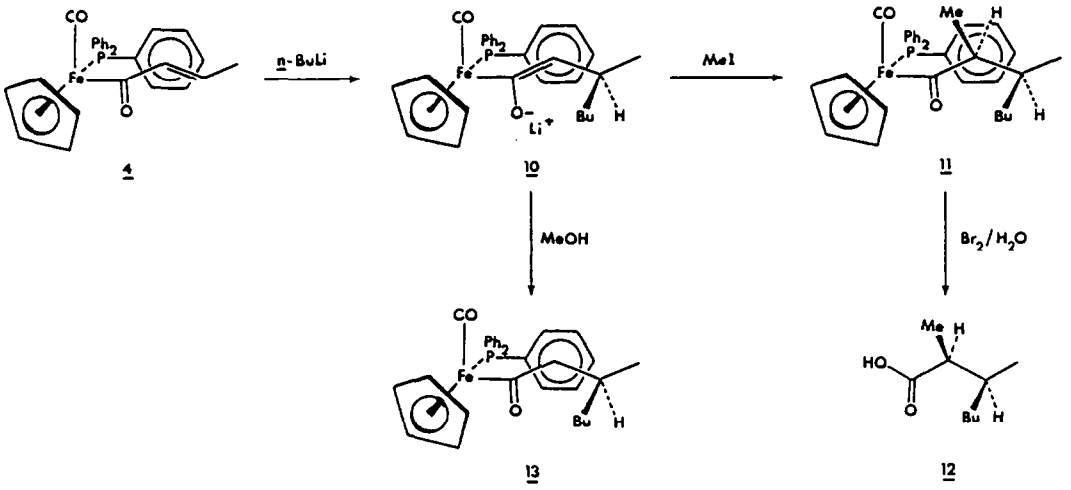
Table 2.

Atomic Coordinates and Equivalent Isotropic Temperature Factors

Atom	x/a	y/b	z/c	U(iso) or U(equiv)
FE(1)	0.17634(3)	0.14239(2)	0.11773(4)	0.0337
P(1)	0.30198(4)	0.13633(3)	0.26907(8)	0.0295
C(1)	0.1725(2)	0.0389(2)	0.1115(4)	0.0419
C(2)	0.1085(3)	0.0014(2)	0.2063(4)	0.0545
C(3)	0.1287(3)	-0.0574(2)	0.2889(5)	0.0638
C(4)	0.0741(4)	-0.0935(3)	0.4046(6)	0.0858
C(5)	0.1209(2)	0.1502(2)	0.2943(4)	0.0435
C(6)	0.1301(2)	0.1357(2)	-0.1376(4)	0.0519
C(7)	0.0743(2)	0.1787(2)	-0.0533(4)	0.0556
C(8)	0.1228(3)	0.2372(2)	0.0125(4)	0.0539
C(9)	0.2078(3)	0.2299(2)	-0.0304(4)	0.0542
C(10)	0.2123(2)	0.1665(2)	-0.1230(4)	0.0520
C(11)	0.3195(2)	0.0579(1)	0.4034(3)	0.0335
C(12)	0.3802(2)	0.0062(2)	0.3794(5)	0.0526
C(13)	0.3889(3)	-0.0519(2)	0.4857(6)	0.0627
C(14)	0.3383(3)	-0.0589(2)	0.6139(5)	0.0579
C(15)	0.2779(3)	-0.0081(2)	0.6399(4)	0.0502
C(16)	0.2676(2)	0.0499(2)	0.5335(4)	0.0425
C(17)	0.3980(2)	0.1379(1)	0.1515(3)	0.0345
C(18)	0.4650(2)	0.1862(2)	0.1844(4)	0.0431
C(19)	0.5360(2)	0.1850(2)	0.0908(4)	0.0517
C(20)	0.5405(2)	0.1362(2)	-0.0349(4)	0.0517
C(21)	0.4736(2)	0.0887(2)	-0.0704(4)	0.0497
C(22)	0.4018(2)	0.0892(2)	0.0215(4)	0.0432
C(23)	0.3231(2)	0.2073(1)	0.4239(3)	0.0348
C(24)	0.3824(2)	0.1985(2)	0.5638(4)	0.0433
C(25)	0.3981(2)	0.2526(2)	0.6779(4)	0.0508
C(26)	0.3556(3)	0.3158(2)	0.6554(5)	0.0548
C(27)	0.2957(3)	0.3252(2)	0.5184(5)	0.0565
C(28)	0.2792(2)	0.2707(2)	0.4040(4)	0.0470
O(1)	0.2214(2)	0.0034(1)	0.0348(3)	0.0567
O(2)	0.0833(2)	0.1601(2)	0.4080(3)	0.0636
H(1)	0.0469(3)	0.0301(2)	0.2234(4)	0.045
H(2)	0.1994(3)	-0.0732(2)	0.2775(5)	0.045
H(3)	0.0607(4)	-0.1344(3)	0.3726(6)	0.045
H(4)	0.0032(4)	-0.0704(3)	0.3734(6)	0.045
H(5)	0.0972(4)	-0.0894(3)	0.5172(6)	0.045
H(6)	0.1167(2)	0.0892(2)	-0.1893(4)	0.045
H(7)	0.0118(2)	0.1687(2)	-0.0455(4)	0.045
H(8)	0.0970(3)	0.2779(2)	0.0630(4)	0.045
H(9)	0.2595(3)	0.2602(2)	-0.0038(4)	0.045
H(10)	0.2592(2)	0.1491(2)	-0.1523(4)	0.045
H(11)	0.4209(2)	0.0151(2)	0.3053(5)	0.045
H(12)	0.4330(3)	-0.0853(2)	0.4592(6)	0.045
H(13)	0.3348(3)	-0.1046(2)	0.6817(5)	0.045
H(14)	0.2332(3)	-0.0164(2)	0.7222(4)	0.045
H(15)	0.2259(2)	0.0851(2)	0.5424(4)	0.045
H(16)	0.4602(2)	0.2229(2)	0.2672(4)	0.045
H(17)	0.5820(2)	0.2185(2)	0.1159(4)	0.045
H(18)	0.5943(2)	0.1315(2)	-0.0834(4)	0.045
H(19)	0.4741(2)	0.0526(2)	-0.1490(4)	0.045
H(20)	0.3523(2)	0.0571(2)	-0.0018(4)	0.045
H(21)	0.4147(2)	0.1570(2)	0.5780(4)	0.045
H(22)	0.4406(2)	0.2503(2)	0.7657(4)	0.045
H(23)	0.3762(5)	0.3583(2)	0.7183(5)	0.045
H(24)	0.2705(3)	0.3680(2)	0.4950(5)	0.045
H(25)	0.2395(2)	0.2785(2)	0.3145(4)	0.045

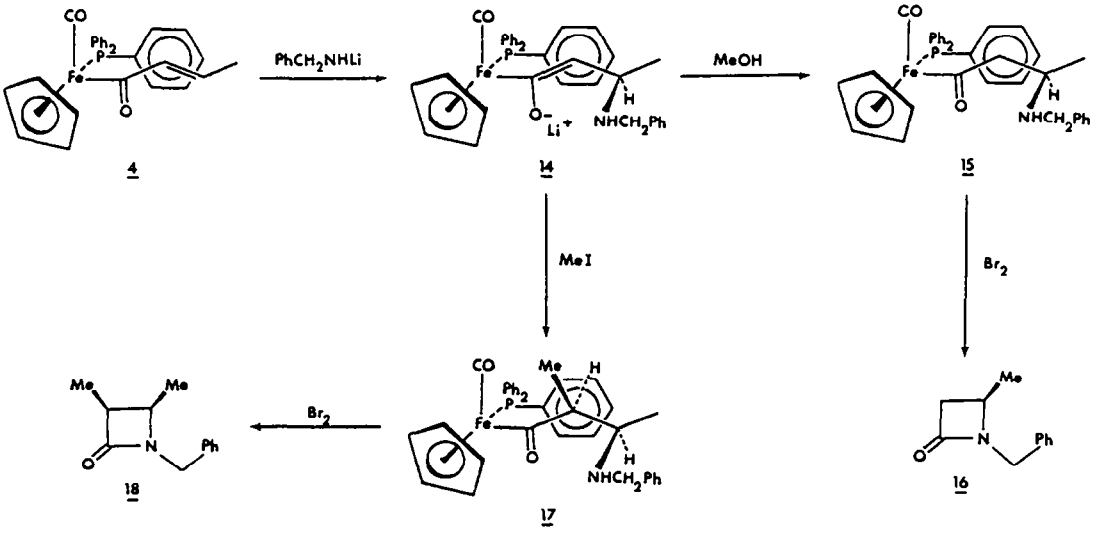
The E-crotonyl iron complex 4 reacted with n-butyllithium to generate the enolate 10 which on addition of methyl iodide gave essentially a single diastereoisomer of the α,β-dimethylheptanoyl complex 11; (d.e. >100:1:1:1 as determined by 300 MHz ^{1}H n.m.r. spectroscopy). The relative configuration in 11 of the iron-centre to the α-chiral centre was established as RS,SR from the chemical shift (δ0.98) of the α-methyl doublet[12] and indicated that as before Michael addition had occurred to 4 in the cisoid conformation. The relative configuration of the β-centre was assigned on the assumption that the n-butyllithium had attacked 4 in the cisoid conformation, with the carbonyl oxygens anti, from the unhindered face. In this way the relative configurations of 11 were assigned as RSS,SRR and this was confirmed by oxidative decomplexation to the known erythro

carboxylic acid.[15] Protonation of enolate 10 with methanol gave complex 13 as a single diastereoisomer assigned as RS,SR by analogy with the formation of RSS,SRR-12.



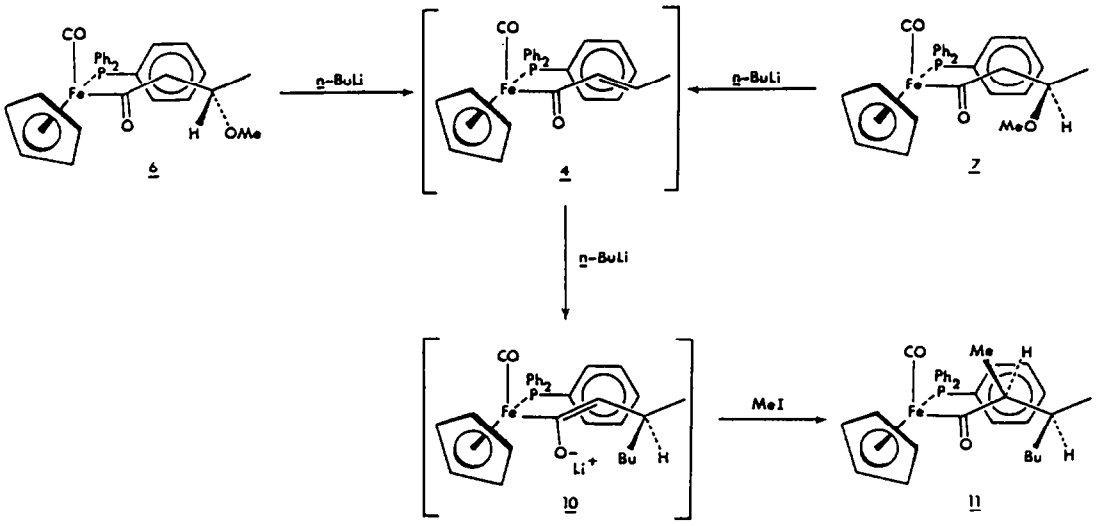
4 10 11 13 12

The extension of this methodology to the formation of racemic β-amino acyl complexes, precursors of β-lactams,[16,18] has been communicated by Liebeskind et.al.[5] We have independently studied this type of reaction. Thus, addition of lithium benzylamide to 4 generated enolate 14 which on protonation gave the β-aminoacyl complex (RR,SS)- 15 as a single diastereoisomer. Decomplexation of 15 gave the known 4-methyl-β-lactam 16.[17,18] Trapping enolate 14 with methyl iodide gave (RSR,SRS)-17 as a single diastereoisomer. The relative configurations in complexes 15 or 17 were assigned by analogy with complexes 13 and 11. Confirmation was provided by the appearance of the α-methyl doublet for 17 at δ1.12 in the ^{1}H n.m.r. spectrum and by oxidative decomplexation of 17 to give the known cis-3,4-dimethyl-β-lactam 18.[18] Epimerisation of 18 by treatment with base gave a 1:2 mixture of 18 and its trans-epimer,[18] thus demonstrating that the cis-β-lactam is the thermodynamically less stable diastereoisomer.

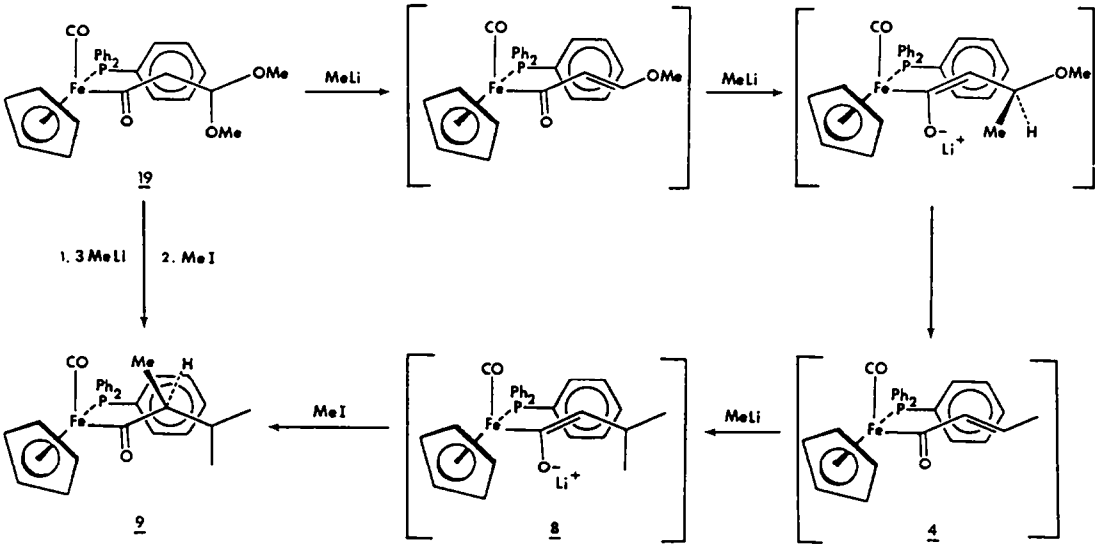


4 14 15 18 17 16

We have shown previously that treatment of the β-methoxy acyl complexes 6 and 7 with the non-nucleophilic base, sodium hydride, results in the elimination of methanol and generates the E-crotonyl iron complex 4.[10] Treatment of either 6 or 7 with two equivalents of n-butyllithium generated the enolate 10. Presumably the first equivalent promotes elimination to generate 4 *in situ* which is then trapped by Michael addition of the second equivalent of n-butyllithium. Subsequent addition of methyl iodide gave 11 again as a single diastereoisomer.



Similarly, treatment of the β-dimethoxy acyl complex[19] 19 with three equivalents of methyllithium followed by addition of methyl iodide yielded complex 9 as a single diastereoisomer. The formation of 9 from 19 is consistent with two sequential elimination-Michael additions giving enolate 8 which is then methylated.

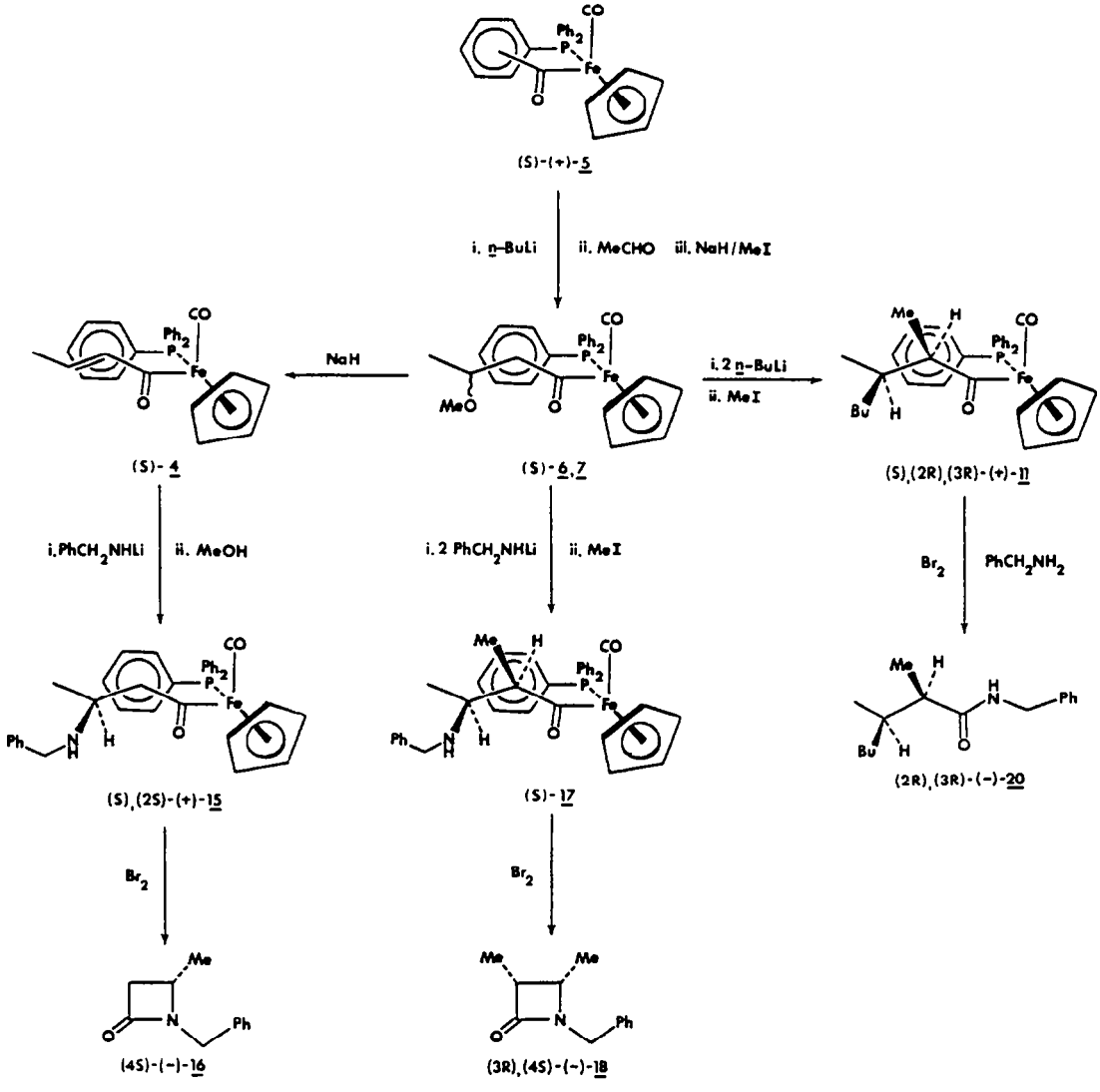


In order to extend the highly diastereoselective tandem Michael addition-alkylations and efficient decomplexation methods described to the asymmetric synthesis of α,β-dialkyl-substituted carbonyl compounds and 4-alkyl- and 3,4-dialkyl-substituted β-lactams, the above reactions were repeated using enantiomerically pure acyl complexes containing the chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$. Thus, the optically pure (S)-(+)-acetyl complex 5, whose absolute configuration we have unambiguously assigned,[20] was treated successively with n-butyllithium and acetaldehyde. The essentially 1:1 mixture of β-hydroxy complexes were O-methylated and the resulting β-methoxy complexes (S)-6 and-7 treated with two equivalents of n-butyllithium followed by methyl iodide. Work-up gave the (S),(2R),(3R)-(+)-2,3-dimethylheptanoyl complex 11 $\{[\alpha]_D^{25}$ + 228.0° (c 0.29, C_6H_6)} (d.e. > 100:1:1:1) whose relative configuration was that as had been deduced previously. Oxidative decomplexation of (S),(2R),(3R)-(+)- 11 with bromine in

dichloromethane at -78°C and in the presence of benzylamine gave (2R),(3R)-(-)-N-benzyl-2,3-dimethylheptanamide 20 {$[\alpha]_D^{\star}$ -5.3° (c 1.23, C_6H_6)} in 81% yield. The amide (2R),(3R)-(-)- 20 was diastereoisomerically pure by 300 MHz ^1H n.m.r. spectroscopy and again confirmed that the decomplexation procedure had occurred with complete retention of stereochemistry at the α-centre in agreement with previously reported cases.[21] It therefore follows that (2R),(3R)-(-)- 20 must have an optical purity of greater than 100:1 and the absolute configuration as stated.

Similarly, addition of two equivalents of lithium benzylamide and then methyl iodide to (S)-6,7 gave the (S)-β-amino-α,β-dimethyl complex 17 as a single diastereoisomer. Without purification, (S)-17 was decomplexed with bromine to the (3R),(4S)-(-)-cis-3,4-dimethyl-N-benzyl-β-lactam 18 {$[\alpha]_D^{\star}$ -29.2° (c 0.69, $CHCl_3$)} in 42% yield. As no trace of the thermodynamically more stable trans isomer could be detected, neither epimerisation at the α- nor β-centres must accompany the decomplexation reaction. This when combined with the fact that the starting (S)-(+)-acetyl complex 5 was optically pure and that the derived complex (S)-17 was formed with high diastereoselectivity (>100:1:1:1) necessitates that (3R),(4S)-(-)-18, not previously known in optically active form, has an optical purity of greater than 100:1 and the absolute configuration as stated.

Finally, in order to confirm the intermediacy of the (S)-E-crotonyl complex 4 in the conversion of (S)-6,7 to complexes (S),(2R),(3R)-(+)-11 and (S)-17, complexes (S)-6,7 were



subjected to sodium hydride-induced elimination of methanol.[19] Complex (S)-4 was isolated together with recovered starting material (S)-6,7 which as an inseparable mixture was treated with lithium benzylamide followed by methanol. A single observable diastereoisomer of the (S),(2S)-(+)-β-amino-β-methyl complex 15 {$[\alpha]_D^{21}$ + 143.0° (c 0.44, C_6H_6)} was obtained as the sole product. Oxidative decomplexation of (S),(2S)-(+)-15 gave the (4S)-(-)-4-methyl-N-benzyl-β-lactam 16 {$[\alpha]_D^{24}$-38.5° (c 2.1, MeOH), lit.,[22] $[\alpha]_D^{21}$-34.5° (c 3.0, MeOH)} in 65% yield. Since no racemisation is expected during the decomplexation step, (4S)-(-)-16 must have an optical purity of greater than 100:1 and the 4S absolute configuration.

The above reactions demonstrate the stereocontrolled tandem addition of nucleophiles and electrophiles to the E-crotonyl iron acyl complex 4. The two new bonds are formed cis onto one of the diastereotopic faces (the unhindered face) of the original carbon-carbon double bond. When used in combination with enantiomerically pure acyl complexes, these reactions also illustrate the potential of the chiral auxiliary [$(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)$] for the asymmetric synthesis of α,β-substituted carbonyl compounds and 3,4-substituted β-lactams of high optical purity. Since a wide range of E-α,β-unsaturated ligands attached to the chiral auxiliary are available[19] and since many electrophiles can be used to quench the enolate generated by the Michael addition of lithium nucleophiles, the scope of this reaction is extensive.

Experimental

All reactions and purifications were performed under a nitrogen atmosphere using standard vacuum line and schlenk tube techniques.[23] All solvents were removed under reduced pressure. Tetrahydrofuran(THF) was dried over sodium benzophenone ketyl and distilled. Dichloromethane was distilled from calcium hydride and hexane refers to that fraction boiling between 67°C and 70°C. n-Butyllithium (1.6M in hexane) and methyllithium (1.5 M in diethyl ether) were used as supplied by Aldrich. Unless otherwise stated, infrared spectra were recorded as Nujol mulls on a Perkin-Elmer 297 instrument. N.m.r. spectra were recorded in $CDCl_3$, on Bruker WH 300 (300.13 MHz ^1H) and Bruker AM 250 (62.896 MHz ^{13}C, 101.26 MHz ^{31}P) spectrometers. Mass spectra were recorded on a V.G. Micromass ZAB 2F instrument using FD techniques. Elemental analyses were performed by the University of Manchester and the Dyson Perrins Laboratory Analytical Services.

X-ray crystal structure analysis of (RS)-E-[$(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)$COCH=CHMe] 4

Cell parameters and reflection intensities were measured with graphite monochromated Mo-Kα radiation on an Enraf-Nonius CAD-4F diffractometer operating in the ω/2θ scan mode for a crystal having approximate dimensions 0.78 x 0.20 x 0.18 mm. The scan range (ω) was calculated from [0.95 + 0.35 tan θ]° and the scan speed varied from 0.9 to 6.7° min^{-1} depending upon the intensity. Reflections were scanned in the range $0 < \theta < 25°$. Three standard reflections measured every hour showed no appreciable variation with time. The data were corrected for Lorentz, polarisation and absorption effects[24] (relative transmission factors 1.00 - 1.22) and equivalent reflections were merged to give 4326 unique reflections (R_{merg} 0.04) of which 2842 were considered to be observed [$I > 3\sigma(I)$] and used in the structure analysis.

Crystal Data, $C_{28}H_{25}O_2PFe$, M = 480.33, monoclinic, a = 15.480 (2), b = 18.904(4), c = 8.055(1) Å, β = 95.63(2)°, U = 2345.8 Å^3, Z = 4, D_c = 1.37 Mgm^{-3}, μ (Mo-Kα = 0.71069 A) 7.30 cm^{-1}, space group $P2_1/n$ (established from systematic absences). The structure was solved by Patterson and electron density methods. Final full-matrix least squares refinement included parameters for atomic positions, temperature factors (anisotropic for non-hydrogen atoms), an overall scale factor and an extinction parameter. All hydrogen atoms were allowed to "ride" on their respective carbon atoms and were assigned a common overall temperature factor. The refinement was terminated when all shifts were less than 0.1 σ with R 0.038 (Rw 0.046). The weight for each reflection was

calculated from the Chebyshev series $w = [955.87\ t_0(X) + 1435.25\ t_1(X) + 579.68\ t_2(X) + 95.21\ t_3(X)]$ where $X = F_o/F_{max}$[25]. Final difference Fourier synthesis showed no significant residual electron density and a detailed analysis failed to reveal any systematic errors. All calculations were performed with the CRYSTALS package on the Chemical Crystallography VAX 11/750 computer.[26] Atomic scattering factors were taken from International Tables, Volume IV.[27] Selected bond lengths and bond angles are given in Table 1. Final atomic positional coordinates with e.s.d.'s in parentheses are listed in Table 1.

Preparation of E-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH=CHMe] 4.

Complex 4 was prepared according to the procedure described previously.[10]

General procedure for the Michael addition of alkyllithiums to E-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH=CHMe] 4 followed by subsequent reaction with electrophiles to give complexes 9, 11 and 13

The alkyllithium (1.2 equivalents) was added to complex 4 (typically 500 mg, 1.04 mmol) in THF (25 ml) at -78°C to give a dark red solution. After stirring (-78°C; 2h for the addition of n-butyllithium and -40°C; 2h for methyllithium), the electrophile (2 equivalents) was added dropwise to the solution at -78°C and the mixture further stirred (-78°C; 2h). Warming to room temperature and removal of solvent gave an orange oil which was extracted with dichloromethane (3 x 10 ml) and filtered through alumina (Grade V). The product complexes were purified by chromatography on alumina (Grade I), analysed by ^{1}H n.m.r. spectroscopy upon removal of solvents to determine diastereoselectivites and obtained as orange needles from hexane (-30°C).

(RS/SR)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(Me)$CHMe_2$] 9.

Elution with diethyl ether gave complex 9 (60%) as a single diastereoisomer. (Found: C, 70.7; H, 6.2; P, 6.2. $C_{30}H_{31}FeO_2P$ requires C, 70.6; H, 6.1; P, 6.1%); ν_{max} 1900 vs (C≡O), 1612 s cm^{-1} (C=O); ^{1}H n.m.r. δ 7.6 - 7.3 (15H, m, Ph), 4.43 (5H, d, J_{PH} 1.3 Hz, C_5H_5), 2.80 (1H, dq, $J_{1,2}$ 7.2 Hz, 2.8 Hz, COCH), 1.41 (1H, dseptets, $J_{1,2}$ 6.8 Hz, 2.8 Hz, C<u>H</u>Me_2), 0.91 (3H, d, $J_{1,2}$ 7.3 Hz, COCH<u>Me</u>), 0.53 (3H, d, $J_{1,2}$ 6.9 Hz, Me), 0.33 (3H, d, $J_{1,2}$ 6.8 Hz, Me); ^{13}C{^{1}H} n.m.r. δ 221.2 (d, J_{PC} 31.5 Hz, C≡O), 136.9 (d, J_{PC} 42.1 Hz, Ph C_{ipso}), 133.5 (d, J_{PC} 9.4 Hz, Ph C_{ortho}), 129.5 (s, Ph C_{para}), 127.9 (d, J_{PC} 9.3 Hz, Ph C_{meta}), 85.2 (s, C_5H_5), 72.4 (s, CO<u>C</u>H), 26.4 (s, <u>C</u>HMe_2), 21.6 (s, Me), 17.1 (s, Me), 10.8 (s. Me); ^{31}P{^{1}H} n.m.r. δ 71.7; <u>m/z</u> 510 (M^+).

(RSS/SRR)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(Me)CH(Me)<u>n</u>-Bu] 11.

Elution with 60:80 petrol-diethyl ether (1:1) gave complex 11 (93%) as a 160:1:<1:<1 mixture of diastereoisomers. (Found: C, 72.0; H, 6.8; P, 5.5. $C_{33}H_{37}FeO_2P$ requires C, 71.7; H, 6.75; P, 5.6%); ν_{max} 1908 vs (C≡O), 1598 s cm^{-1} (C=O); ^{1}H n.m.r. δ 7.6 - 7.3 (15H, m, Ph), 4.42 (5H, d, J_{PH} 1.4 Hz, C_5H_5), 2.77 (1H, dq, $J_{1,2}$ 7.3 Hz, 3.0 Hz, COCH), 1.26 - 0.61 (7H, m, $CH(CH_2)_3$), 0.97 (3H, d, $J_{1,2}$ 7.4 Hz, COCH<u>Me</u> major diastereoisomer), 0.82 (3H, t, $J_{1,2}$ 6.9 Hz, CH_2<u>Me</u>), 0.47 (3H, d, $J_{1,2}$ 6.8 Hz, CH<u>Me</u>), 0.23 (3H, d, $J_{1,2}$ 6.9 Hz, COCH<u>Me</u> minor diastereoisomer); ^{13}C{^{1}H} n.m.r. δ 221.2 (d, J_{PC} 31.4 Hz, C≡O), 136.9 (d, J_{PC} 42.3 Hz, Ph C_{ipso}), 133.4 (d, J_{PC} 9.5 Hz, Ph C_{ortho}), 129.4 (s, Ph C_{para}), 127.9 (d, J_{PC} 9.4 Hz, Ph C_{meta}), 85.2 (s, C_5H_5), 72.7 (d, J_{PC} 4.4 Hz, CO<u>C</u>H), 32.4 (s, CH), 31.3 (s, CH_2), 30.0 (s, CH_2), 23.1 (s, CH_2), 18.2 (s, Me), 14.3 (s, Me), 11.8 (s, Me); ^{31}P{^{1}H} n.m.r. δ 71.8; <u>m/z</u> 552 (M^+).

(RS/SR)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2$CH(Me)<u>n</u>-Bu] 13

Elution with diethyl ether gave complex 13 (82%) as a >180:1 mixture of diastereoisomers. (Found: C, 71.55; H, 6.9; P, 5.8. $C_{32}H_{35}FeO_2P$ requires C, 71.4; H, 6.55; P, 5.75%); ν_{max} 1905 vs (C≡O), 1620 s cm^{-1} (C=O); ^{1}H n.m.r. δ 7.6 - 7.3 (15H, m, Ph), 4.40 (5H, d, J_{PH} 1.1 Hz, C_5H_5), 2.91, 2.34 (2H, ABX system, J_{AB} 16.6 Hz, $COCH_2$), 1.70 - 0.89 (7H, m, $CH(CH_2)_3$), 0.86 (3H, t, $J_{1,2}$ 7.0 Hz, CH_2<u>Me</u>), 0.41 (3H, d, $J_{1,2}$ 6.6 Hz, CH<u>Me</u>); ^{13}C{^{1}H} n.m.r. δ 220.8 (d, J_{PC} 31.4 Hz, C≡O), 136.7 (d, J_{PC} 42.9 Hz, Ph C_{ipso}), 133.4 (d, J_{PC} 9.5 Hz, Ph C_{ortho}), 129.6 (s, Ph C_{para}), 128.0 (d, J_{PC} 9.3 Hz, Ph C_{meta}) 85.3 (s, C_5H_5), 74.1 (d, J_{PC} 4.8 Hz, $CO\underline{C}H_2$), 36.8 (s, CH_2), 29.3 (s, CH), 29.3 (s, CH_2) 23.0 (S, CH_2), 19.7 (s, Me), 14.1 (s, Me); ^{31}P{^{1}H} n.m.r. δ 72.4; <u>m/z</u> 538 (M^+).

Oxidative decomplexation of (RSS/SRR)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(Me)CH(Me)n-Bu] 11 to erythro-2,3-dimethylheptanoic acid 12

Bromine (0.1 ml, 1.9 mmol) in THF (2 ml) was added dropwise to a cooled (0°C) solution of complex 11 (566 mg, 1.03 mmol) in THF (10 ml) containing water (0.4 ml) to give a dark brown solution. After stirring (0°C; 3h), a saturated $Na_2S_2O_3$ (aq) solution (1 ml) was added and the THF removed. Upon further addition of water (15 ml) and acidification (pH 1), the aqueous solution was extracted with diethyl ether (3 x 20 ml). The resultant green solution was concentrated (20 ml) and washed successively with saturated $NaHCO_3$ (aq) (20 ml) and then water (2 x 20 ml). The combined aqueous washings were reacidified (pH 1) and extracted with diethyl ether (3 x 15 ml). The extracts were washed with water (20 ml) and dried (anhydrous Na_2SO_4). Removal of solvent gave a pale yellow oil which was chromatographed on silica gel (60H-Merck) to give upon elution with diethyl ether erythro-2,3-dimethylheptanoic acid 12 (44 mg, 27%).[18] ν_{max} ($CHCl_3$) 3500 br (O-H), 1700 vs cm^{-1} (C=O); ^1H n.m.r. δ 2.35 (1H, quintet, $J_{1',2}$ 6.7 Hz, CHCO$_2$H), 1.75 (1H, m, CH(Me)CH$_2$), 1.47-0.82 (6H, m, (CH$_2$)$_3$), 1.11 (3H, d, $J_{1',2}$ 7.1 Hz, CH(Me)CO$_2$H), 0.92 (3H, d, $J_{1',2}$ 6.8 Hz, CH(Me)CH$_2$), 0.87 (3H, t, $J_{1',2}$ 6.9 Hz, CH$_2$CH$_3$); $^{13}C\{^1H\}$ n.m.r. δ 181.6 (CO$_2$H), 44.5 (CHCO$_2$H), 35.8 (CH), 32.9 (CH$_2$), 29.2 (CH$_2$), 22.8 (CH$_2$), 17.1 (Me), 14.0 (Me), 13.6 (Me); m/z (CI/NH$_3$) 176 (M^+ + 18).

General procedure for the Michael addition of lithium benzylamide to E-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH=CHMe] 4 followed by subsequent reaction with electrophiles to give complexes 15 and 17

n-Butyllithium (0.4 ml, 0.64 mmol) was added to benzylamine (70 mg, 0.66 mmol) in THF (20 ml) at -20°C to give an intense purple solution. The solution was stirred (-20°C; 1h), cooled to -78°C and added dropwise to complex 4 (250 mg, 0.52 mmol) in THF (30 ml) at -78°C to give a deep red solution. After stirring (-78°C; 2h), the electrophile (4 equivalents) was added and the mixture further stirred (-78°C; 1h). Warming to room temperature and removal of solvent gave an orange solid which was dissolved in dichloromethane and filtered through Celite. The product complexes were purified by chromatography on alumina (Grade I), analysed by ^1H n.m.r. spectroscopy upon removal of solvents to determine diastereoselectivities and obtained as orange needles from dichloromethane-hexane.

(RR/SS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH$_2$CH(Me)NHCH$_2$Ph] 15.

Elution with dichloromethane-ethyl acetate-methanol (10:9:1) gave complex 15 (90%) as a single diastereoisomer. (Found: C, 71.6; H, 5.8; N, 2.4; P, 5.0. $C_{38}H_{34}FeNO_2P$ requires C, 71.55; H, 5.8; N, 2.4; P, 5.3%); ν_{max} 3300 w,br (N-H), 1910 vs (C≡O), 1600 s cm^{-1} (C=O); ^1H n.m.r. δ 7.6 -7.2 (20H, m, Ph), 4.40 (5H, d, J_{PH} 1.1 Hz, C_5H_5), 3.69, 3.56 (2H, AB system, J_{AB} 12.9 Hz, CH$_2$Ph), 3.08, 2.68 (2H, ABX system, J_{AB} 18.3 Hz, COCH$_2$), 2.64 (1H, m, CHMe), 0.68 (3H, d, $J_{1',2}$ 6.1 Hz, Me); $^{13}C\{^1H\}$ n.m.r. δ 220.5 (d, J_{PC} 31.4 Hz, C≡O), 141.1 (s, CH$_2$Ph C_{ipso}), 136.5 (d, J_{PC} 42.6 Hz, Ph C_{ipso}), 133.4 (d, J_{PC} 9.4 Hz, Ph C_{ortho}), 129.7 (s, Ph C_{para}), 128.2 (s, CH$_2$Ph C_{ortho}), 128.1 (d, J_{PC} 8.5 Hz, Ph C_{meta}), 126.6 (s, CH$_2$Ph C_{para}), 85.4 (s, C_5H_5), 73.2 (d, J_{PC} 5.4 Hz, COCH$_2$), 51.3 (s, CH$_2$Ph), 49.7 (s, CHMe), 20.0 (s, Me); $^{31}P\{^1H\}$ n.m.r. δ 72.2; m/z 587 (M^+).

(RSR/SRS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(Me)CH(Me)NHCH$_2$Ph] 17.

Elution with dichloromethane-ethyl acetate-methanol (10:9:1) gave complex 17 (91%) as a single diastereoisomer. (Found: C, 71.9; H, 6.0; N, 2.4; P, 5.1. $C_{39}H_{36}FeNO_2P$ requires C, 71.9; H, 6.0; N, 2.3; P, 5.15%); ν_{max} 3330 w (N-H), 1910 vs (C≡O), 1580 s cm^{-1} (C=O); ^1H n.m.r. δ 7.5 -7.2 (20H, m, Ph), 4.44 (5H, d, J_{PH} 1.2 Hz, C_5H_5), 3.67, 3.32 (2H, AB system, J_{AB} 13.9 Hz, CH$_2$Ph), 2.68 (1H, m, COCH), 1.72 (1H, m, CH(Me)N), 1.12 (3H, d, $J_{1',2}$ 7.5 Hz, CH(Me)N), 0.54 (3H, d, $J_{1',2}$ 6.4 Hz, COCH(Me)); $^{13}C\{^1H\}$ n.m.r. δ 220.7 (d, J_{PC} 31.5 Hz, C≡O), 141.3 (s, CH$_2$Ph C_{ipso}), 136.4 (d, J_{PC} 42.6 Hz, Ph C_{ipso}), 133.2 (d, J_{PC} 9.5 Hz, Ph C_{ortho}), 129.5 (s, Ph C_{para}), 127.9 (d, J_{PC} 9.1 Hz, Ph C_{meta}), 126.1 (s, CH$_2$Ph C_{para}), 85.5 (s, C_5H_5), 71.5 (d, J_{PC} 5.2 Hz, COCH), 51.2 (s, CH(Me)N), 51.1 (s, CH$_2$Ph), 17.5 (s, CH(Me)N), 10.0 (s, COCH(Me)); $^{31}P\{^1H\}$ n.m.r. δ 70.7; m/z 601 (M^+).

General procedure for the oxidative decomplexation of complexes 15 and 17 to β-lactams

Bromine (2 equivalents) in dichloromethane (2 ml) was added dropwise to a solution of the β-amino acyl complex (typically 500 mg) in dichloromethane (15 ml) at -78°C to give a brown-red solution. After stirring (-78°C; 1h), triethylamine (excess) was added and the mixture warmed to room temperature. Removal of solvent (below 20°C) gave a tacky green solid. Short path distillation of this residue under reduced pressure (100°C, 0.1 mmHg) afforded the crude β-lactam which was further purified by chromatography on silica gel (60H-Merck).

(±)-4-Methyl-1-(phenylmethyl)-azetidin-2-one 16.

Elution with acetone-diethyl ether (1:9) gave β-lactam 16 (68%) as a colourless oil. ν_{max} (neat) 1750 s cm^{-1} (C=O) [lit.[18] 1750 cm^{-1}]; ^1H n.m.r. δ 7.3 - 7.2 (5H, m, Ph), 4.60, 4.11 (2H, AB system, J_{AB} 15.2 Hz, CH_2Ph), 3.58 (1H, m, CHMe), 3.07, 2.54 (2H, ABX system, J_{AB} 14.4 Hz, J_{AX} trans 2.1 Hz, J_{AX} cis 4.9 Hz, $COCH_2$), 1.22 (3H, d, $J_{1,2}$ 6.1 Hz, Me) [lit.[18] δ 7.3 (5H, s, Ph), 4.65, 4.06 (2H, d, $J_{1,2}$ 15 Hz, CH_2Ph), 3.56 (1H, m, CHMe), 3.05 (1H, dd, $J_{1,2}$ 4.9 Hz, 14.5 Hz, $COCH_2$), 2.48 (1H, dd, $J_{1,2}$ 2.5 Hz, 14.5 Hz, $COCH_2$), 1.17 (3H, d, $J_{1,2}$ 6 Hz, Me)]; $^{13}C\{^1H\}$ n.m.r. δ 166.8 (C=O), 136.1 (Ph C_{ipso}), 128.7 (Ph C_{meta}/C_{ortho}), 128.2 (Ph C_{ortho}/C_{meta}), 127.6 (Ph C_{para}), 47.0 (CHMe), 44.4 (CH_2), 44.2 (CH_2), 18.5 (Me); m/z 175 (M^+).

(±)-cis-3,4-Dimethyl-1-(phenylmethyl)-azetidin-2-one 18.

Elution with acetone-diethyl ether (1:9) gave β-lactam 18 (69%) as a colourless oil. ν_{max} (neat) 1740 s cm^{-1} (C=O); ^1H n.m.r. δ 7.4 - 7.2 (5H, m, Ph), 4.59, 4.04 (2H, AB system, J_{AB} 15.2 Hz, CH_2Ph), 3.63 (1H, dq, $J_{1,2}$ 6.4 Hz, 5.4 Hz, CH(Me)N), 3.22 (1H, dq, $J_{1,2}$ 7.6 Hz, 5.4 Hz, COCH(Me)), 1.16 (3H, d, $J_{1,2}$ 7.6 Hz, COCH(Me)), 1.07 (3H, d, $J_{1,2}$ 6.4 Hz, CH(Me)N) [lit[18] δ 7.23 (5H, m, Ph), 4.52, 4.00 (2H, d, $J_{1,2}$ 15.5 Hz, CH_2Ph), 3.51 (1H, m, $J_{1,2}$ 6.3 Hz, 6.0 Hz, CH(Me)N), 3.13 (1H, m, $J_{1,2}$ 7.5 Hz, 6.0 Hz, COCH), 1.11 (3H, d, $J_{1,2}$ 7.5 Hz, Me), 1.01 (3H, d, $J_{1,2}$ 6.3 Hz, Me)]; $^{13}C\{^1H\}$ n.m.r. δ 171.2 (C=O), 136.2 (Ph C_{ipso}), 128.7 (Ph C_{ortho}/C_{meta}), 128.2 (Ph C_{meta}/C_{ortho}), 127.6 (Ph C_{para}), 50.5 (COCH), 47.0 (CH(Me)N), 43.9 (CH_2Ph), 13.5 (COCH(Me)), 8.8 (CH(Me)N); m/z 189 (M^+).

Epimerisation of (±)-cis-3,4-Dimethyl-1-(phenylmethyl)-azetidin-2-one 18

The cis-β-lactam 18 (80 mg, 0.42 mmol) and potassium tert-butoxide (10 mg, 0.09 mmol) in tert-butanol (4 ml) were heated (50°C; 15 h). The reaction mixture was poured into water (5 ml) and extracted with diethyl ether (3 x 4 ml). The ether extracts were dried (anhydrous Na_2SO_4) and upon evaporation gave a colourless oil (75 mg, 95%) identified by ^1H n.m.r. spectroscopy as a 1:2 mixture of 18 and its trans-epimer.[18] ^1H n.m.r. δ 7.4 - 7.2 (5H, m, Ph), 4.61, 4.07 (2H, AB system, J_{AB} 15.2 Hz, CH_2Ph), 3.15 (1H,dq, $J_{1,2}$ 6.1 Hz, 2.0 Hz, $CHCH_3$), 2.73 (1H,dq, $J_{1,2}$ 7.4 Hz, 1.5 Hz, $CHCH_3$), 1.27 (3H, d, $J_{1,2}$ 7.4 Hz, CH_3), 1.20 (3H,d, $J_{1,2}$ 6.1 Hz, CH_3) [lit.[18] δ 7.28 (5H, s, Ph), 4.62, 4.05 (2H, AB system, J_{AB} 15 Hz, CH_2 Ph), 3.16 (1H,dq, $J_{1,2}$ 6 Hz , 2 Hz, NCH), 2.74 (1H, dq, $J_{1,2}$ 6 Hz, 2 Hz, CHCO), 1.25 (3H, d, $J_{1,2}$ 6 Hz, CH_3), 1.17 (3H, d, $J_{1,2}$ 6 Hz, CH_3)].

Preparation of (RSS/SRR)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(Me)CH(Me)n-Bu] 11 from both (RS/SR)- and (RR/SS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2$CH(OMe)Me] 6 and 7

n-Butyllithium (0.6 ml, 0.96 mmol) was added to complex 6 (190 mg, 0.37 mmol) in THF (20 ml) at -78°C to give a dark red solution. After stirring (-78°C; 2.5 h), methyl iodide (0.5 ml; 8.03 mmol) was added in one portion and the mixture further stirred (-78°C; 3h). Addition caused the solution to revert back to an orange colour instantaneously. Warming to room temperature and removal of solvent gave an orange oil which was extracted with dichloromethane (2 x 20 ml) and filtered through alumina (Grade V). Complex 11 (158 mg, 77%) was obtained as an orange powder upon removal of solvent and shown to be single diastereoisomer by comparison of its ^1H n.m.r. spectrum with that of an authentic sample.

The above procedure was repeated with complex 7 (150 mg, 0.29 mmol) and n-butyllithium (0.5 ml, 0.80 mmol). The product complex 11 (144 mg, 89%) was again shown to consist of a single diastereoisomer by ^1H n.m.r. spectroscopy.

Preparation of (RS/SR)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(Me)$CHMe_2$] 9 from [(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OMe)_2$] 19

Methyllithium (1.3 ml, 2.02 mmol) was added to complex 19[19] (255 mg, 0.48 mmol) in THF (20 ml) at -78°C. The solution, upon warming to -40°C and stirring (2h), became dark red in colour. After recooling (-78°C), methyl iodide (0.4 ml, 6.42 mmol) was added in one portion to give a light orange solution which was further stirred (-78°C; 2h). Warming to room temperature and removal of solvent gave an orange oil which was extracted with dichloromethane (2 x 20 ml) and filtered through alumina (Grade V). Chromatography on alumina (Grade I) gave upon elution with diethyl ether and removal of solvent complex 9 (124 mg, 50%) as a single diastereoisomer as shown by ^{1}H n.m.r. spectroscopy.

Preparation of (SR)- and (SS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OMe)Me$] 6 and 7 from (S)-(+)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COMe] 5

n-Butyllithium (2.1 ml, 3.1 mmol) was added to (S)-(+)-5[20] (1.0 g, 2.2 mmol) in THF (30 ml) at -78°C and the resulting dark red mixture stirred (-78°C; 1h). A solution of acetaldehyde (0.4 ml, 7.2 mmol) in THF (2 ml) was added dropwise. After further stirring (-78°C; 2h), methanol (0.5 ml) was added and the solution warmed to room temperature. Removal of solvents, extraction with dichloromethane (3 x 20 ml) and filtration through alumina (Grade V) gave an orange solution which was concentrated and chromatographed on alumina (Grade I). Elution with dichloromethane-ethyl acetate (1:1) gave starting material 5 identified by comparison with an authentic sample. Elution with dichloromethane-methanol (10:1) gave a 1.4:1 diastereoisomeric mixture of the corresponding β-hydroxy complexes (SS)- and (SR)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OH)Me$] (1.04 g, 95%) identified by comparison of the spectroscopic values with the literature values.[1] This mixture was combined with sodium hydride (200 mg, 8.3 mmol), THF (30 ml) was added and the reaction stirred (20°C, 0.5h). Addition of methyl iodide (1.1 ml, 16.9 mmol), further stirring (20°C; 40h) and removal of solvents gave an orange oil which was extracted with dichloromethane (3 x 30 ml) and filtered through alumina (Grade V). Concentration and chromatography on alumina (Grade I) gave a single yellow band eluted with dichloromethane-ethyl acetate (4:1) identified as a 1:1.4 mixture of (SR)- and (SS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OMe)Me$] 6 and 7 by ^{1}H n.m.r. spectroscopy.[10]

Preparation of (S)-E-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH=CHMe] 4

THF (20 ml) was added to the mixture of (SR)- and (SS)- [(η^5-C_5H_5)Fe(CO)(PPh_3)-$COCH_2CH(OMe)Me$] 6 and 7 (855 mg, 1.67 mmol) and sodium hydride (150 mg, 6.3 mmol) and the reaction stirred (20°C; 48h). Removal of solvent, extraction with dichloromethane (3 x 10 ml) and filtration through alumina (Grade V) gave an orange solution which was chromatographed on alumina (Grade I). A single yellow band was eluted with dichloromethane-ethyl acetate (1:1) which upon removal of solvent gave an orange powder (700 mg) identified by ^{1}H n.m.r. spectroscopy as a 2:1 mixture of (S)-E-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH=CHMe] 4[10] and starting material 6-7. This mixture was used without further purification.

Preparation of (2R),(3R)-(-)-N-benzyl-2,3-dimethylheptanamide 20

(S),(2R),(3R)-(+)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(Me)CH(Me)n-Bu] 11 was prepared from (SR)- and (SS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OMe)Me$] 6 and 7 by an identical procedure to that described above. Thus (SR)-6 and (SS)-7 (356 mg, 0.70 mmol), n-butyllithium (1.0 ml, 1.6 mmol) and methyl iodide (0.4 ml, 6.4 mmol) gave (S),(2R),(3R)-(+)-11 (317 mg, 81%), $[\alpha]_D^{25}$ + 228.0° (c, 0.29, C_6H_6). Bromine (0.04 ml, 0.78 mmol) in dichloromethane (2 ml) was added dropwise to a solution of (S),(2R),(3R)-(+)-11 (317 mg, 0.57 mmol) in dichloromethane (15 ml) at -40°C to give a dark brown solution. After stirring (-40°C; 1h), benzylamine (0.13 ml, 1.2 mmol) was added and the mixture

warmed to room temperature. The solution was concentrated and chromatographed on silica gel (60H-Merck). Elution with 40:60 petrol-diethyl ether (2:1) and removal of solvent gave a green solid identified as [(η^5-C_5H_5)Fe(CO)(PPh_3)Br] by comparison with an authentic sample. Elution with 40:60 petrol-diethyl ether (1:2) and removal of solvent gave white crystals of (2R),(3R)-(-)-N-benzyl-2,3-dimethylheptanamide 20 (114 mg, 81%), (Found: C, 77.5; H, 10.4; N, 5.6. $C_{16}H_{25}NO$ requires C, 77.7; H, 10.2; N, 5.7%; $[\alpha]_D^{24}$ - 5.3° (c, 1.23, C_6H_6); ν_{max} ($CHCl_3$) 3450 m (N-H), 1660 s cm^{-1}(C=O); ^{1}H n.m.r. δ 7.36-7.26 (5H, m, Ph), 5.72 (1H, br, NH), 4.45 (2H, m, CH_2Ph), 2.02 (1H, quintet, $J_{1,2}$ 7.1 Hz, COCH), 1.70-1.00 (7H, m, $CH(CH_2)_3$), 1.14 (3H, d, $J_{1,2}$ 7.0 Hz, CHMe), 0.91 (3H, d, $J_{1,2}$ 6.7 Hz, CHMe), 0.89 (3H, t, $J_{1,2}$ 7.0 Hz, CH_2Me); m/z (ACE/NH_3) 247 (M^+), 91 (M^+-156).

Preparation of (3R),(4S)-(-)-cis-3,4-dimethyl-N-benzyl-β-lactam 18

An identical procedure to that described for the addition of lithium benzylamide to complex 4 was followed. Thus, lithium benzylamide generated from benzylamine (0.35 ml, 3.2 mmol) and n-butyllithium (1.4 ml, 2.24 mmol), and methyl iodide (0.4 ml, 6.4 mmol) was added to (SR)-6 and (SS)-7 (501 mg, 0.98 mmol) to give (S)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COCH(Me)CH(Me)$NHCH_2Ph$] 17 (153 mg, 26%) as a single diastereoisomer. Oxidative decomplexation following the general procedure described above gave the (3R),(4S)-(-)-cis-3,4-dimethyl-N-benzyl-β-lactam 18 (20 mg, 42%), $[\alpha]_D^{24}$ -29.2° c, 0.69, $CHCl_3$) identical in all respects to (±)-18 synthesised above.

Preparation of (4S)-(-)-4-methyl-N-benzyl-β-lactam 16

Following the procedure described above, lithium benzylamide generated from benzylamine (0.3 ml, 2.75 mmol) and n-butyllithium (1.5 ml, 2.4 mmol), and methanol (0.8 ml) was added to the 2:1 mixture of (S)-4 and (SR)-6 - (SS)-7 (700 mg) obtained previously. Work-up gave (S),(2S)-(+)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2$CH(Me)$NHCH_2Ph$] 15 (690 mg, 81%), $[\alpha]_D^{21}$ + 143.0° (c 0.44, C_6H_6) identified by comparison with an authentic sample. Oxidative decomplexation following the general procedure described above gave the (4S)-(-)-4-methyl-N-benzyl-β-lactam 16 (106 mg, 65%), $[\alpha]_D^{24}$ -38.5° (c 2.1, MeOH) {lit.,[22] $[\alpha]_D^{21}$ -34.5° (c 3.0, MeOH)} identical in all respects to (±)- 16 synthesised previously.

Acknowledgements: We thank the SERC for a studentship (to J.C.W.) and financial support (to I.M.D-H, K.H.S. and R.H.J.).

References

1. G.J. Baird and S.G. Davies, J. Organometal. Chem., 1983, 248, C1; G.J. Baird, J.A. Bandy, S.G. Davies, and K. Prout, J. Chem. Soc., Chem. Commun., 1983, 1202; K. Broadley and S.G. Davies, Tetrahedron Lett., 1984, 25, 1743; S.G. Davies, I.M. Dordor, and P. Warner, J. Chem. Soc., Chem. Commun., 1984, 956; S.G. Davies, I.M. Dordor-Hedgecock, P. Warner, R.H. Jones, and K. Prout, J. Organometal. Chem., 1985, 285, 213; S.G. Davies and P. Warner, Tetrahedron Lett., 1985, 26, 4815; S.L. Brown, S.G. Davies, P. Warner, R.H. Jones, and K. Prout, J. Chem. Soc., Chem. Commun., 1985, 1446; S.L. Brown, S.G. Davies, D.F. Foster, J.I. Seeman, and P. Warner, Tetrahedron Lett., 1986, 27, 623.
2. L.S. Liebeskind and M.E. Welker, Organometallics, 1983, 2, 194; L.S. Liebeskind and M.E. Welker, Tetrahedron Lett., 1984, 25, 4341; L.S. Liebeskind, M.E. Welker, and V. Goedken, J. Am. Chem. Soc.,1984, 106, 441.
3. S.G. Davies and J.C. Walker, J. Chem. Soc., Chem. Commun., 1985, 209.
4. S.G. Davies, R.J.C. Easton, K.H. Sutton, J.C. Walker, and R.H. Jones, submitted for publication.
5. L.S. Liebeskind and M.E. Welker, Tetrahedron Lett., 1985, 26, 3079.
6. J.D. Morrison 'Asymmetric Synthesis', Academic Press, New York, Vol.2, 1983, pp. 201-241 and Vol. 3, 1984, pp. 252-267.

7. K. Tomioka, F. Masumi, T. Yamashita, and K. Koga, Tetrahedron Lett., 1984, 25, 333; K. Tomioka, H. Kawasaki, Y. Iitaka, and K. Koga, Tetrahedron Lett., 1985, 26, 903; K. Tomioka, H. Kawasaki, and K. Koga, Tetrahedron Lett., 1985, 26, 3027; A.I. Meyers and B.A. Barner, J. Org. Chem., 1986, 51, 120; J. Nokami, T. Ono, and S. Wakabayshi, Tetrahedron Lett., 1985, 26, 1985; Y. Fukutani, K. Maruka, and H. Yamamoto, Tetrahedron Lett., 1984, 25, 5911; C. Iwata, K. Hattori, S. Uchida, and T. Imanishi, Tetrahedron Lett., 1984, 25, 2995; C. Iwata, M. Fujita, K. Hattori, and S. Uchida, Tetrahedron Lett., 1985, 26, 2221; G.H. Posner and E. Asirvatham, J. Org. Chem., 1985, 50, 2589; G.H. Posner and M. Hulce, Tetrahedron Lett., 1984, 25, 379; G.H. Posner, T.P. Kogan, and M. Hulce, Tetrahedron Lett., 1984, 25, 383; G.H. Posner, L.L. Frye, and M. Hulce, Tetrahedron, 1984, 40, 1401.
8. J. Fujiwara, Y. Fukutani, M. Hasegawa, K. Maruoka, and H. Yamamoto, J. Am. Chem. Soc., 1984, 106, 5004; S. Hashimoto, N. Komeshima, S. Yamada, and K. Koga, Chem. Pharm. Bull., 1979, 27, 2437; T. Mukaiyama and N. Iwasawa, Chem. Lett., 1981, 913; T. Kogure and E.L. Eliel, J. Org. Chem., 1984, 49, 576; P. Mangeney, A. Alexakis, and J.F. Normant, Tetrahedron Lett., 1983, 24, 373; T. Mukaiyama, T. Takeda, and K. Fujimoto, Bull. Chem. Soc. Jpn., 1978, 51, 3368; A.I. Meyers, R.K. Smith, and C.E. Whitten, J. Org. Chem., 1979, 44, 2250; K. Soai, H. Machida, and A. Ookawa, J. Chem. Soc., Chem. Commun., 1985, 469; K. Tomioka, T. Sueuaga, and K. Koga, Tetrahedron Lett., 1986, 27, 369.
9. W. Oppolzer and H.J. Loher, Helv. Chim. Acta., 1981, 64, 2808; W. Oppolzer, R. Moretti, T. Godel, A Meunier, and H. Loher, Tetrahedron Lett., 1983, 24, 4971; W. Oppolzer, P. Dudfield, T. Stevenson, and T. Godel, Helv. Chim. Acta., 1985, 68, 212; W. Oppolzer and T. Stevenson, Tetrahedron Lett., 1986, 27, 1139; G. Helmchen and G. Wegner, Tetrahedron Lett., 1985, 26, 6051.
10. S.G. Davies, R.J.C. Easton, J.C. Walker, and P. Warner, J. Organometal. Chem., 1985, 296, C40; S.G. Davies, R.J.C Easton, J.C. Walker, and P. Warner, Tetrahedron, 1986, 42, 175.
11. L.S. Liebeskind, R.W. Fengl, and M.E. Welker, Tetrahedron Lett., 1985, 26, 3075.
12. S.G. Davies, I.M. Dordor, J.C. Walker, and P. Warner, Tetrahedron Lett., 1984, 25, 1333.
13. S.G. Davies and J.I. Seeman, Tetrahedron Lett., 1984, 25, 1845; S.G. Davies, J.I. Seeman, and I. H. Williams, Tetrahedron Lett., 1986, 27, 619.
14. S.G. Davies and J.I. Seeman, unpublished results.
15. Y. Yamamoto and K. Maruyama, J. Chem. Soc., Chem. Commun., 1984, 904. We thank Professor Yamamoto for providing spectroscopic data on erythro- and threo- 2,3-dimethylheptanoic acid.
16. S.R. Berryhill and M. Rosenblum, J. Org. Chem., 1980, 45, 1984.
17. F.F. Blicke and W.A. Gould, J. Org. Chem., 1958, 23, 1102; I. Ojima and H.B. Kwon, Chem. Lett., 1985, 1327.
18. P.K. Wong, M. Madhavarao, D.F. Marten, and M. Rosenblum, J. Am. Chem. Soc., 1977, 99, 2823.
19. N. Aktogu, H. Felkin, G.J. Baird, S.G. Davies, and O. Watts, J. Organometal. Chem., 1984, 262, 49.
20. S.G. Davies, I.M. Dordor-Hedgecock, K.H. Sutton, J.C. Walker, C. Bourne, R.H. Jones, and K. Prout, J. Chem. Soc., Chem. Commun., 1986, 607.
21. R.W. Johnson and R.G. Pearson, J. Chem. Soc., Chem. Commun. 1970, 986; S.G. Davies, I.M. Dordor-Hedgecock, and P. Warner, Tetrahedron Lett., 1985, 26, 2125; P.W. Ambler and S.G. Davies, Tetrahedron Lett., 1985, 26, 2129.
22. H. Bestian and H. Jensen, Ger. Pat., 1970, 1 807, 498.
23. D.F. Schriver, 'The Manipulation of Air-Sensitive Compounds', McGraw-Hill, New York, 1969.
24. A.C.T. North, D.C. Phillips, and F.S. Mathews, Acta. Crystallogr. Sect. A., 1968, 24, 351.
25. J.R. Carruthers, and D.J. Watkin, Acta. Crystallogr. Sect. A., 1979, 35, 698.
26. J.R. Curruthers, and D.J. Watkin, "CRYSTALS User Guide", Issue 9, Chemical Crystallography Laboratory, University of Oxford, 1985.
27. "International Tables for X-ray Crystallography", Volume IV, pgs. 99-101, 149-150, Kynoch Press, Birmingham, England, 1974.