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Stereoselective Synthesis of (3*R*,4*S*)-Statine Utilising the Iron Acetyl Complex [(η^5-C_5H_5)Fe(CO)(PPh_3)COMe] as a Chiral Acetate Enolate Equivalent.†

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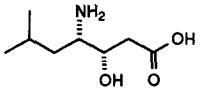
Abstract: Diethylaluminium enolates derived from the iron acetyl complex [(η^5-C_5H_5)Fe(CO)(PPh_3)COMe] undergo highly diastereoselective aldol reactions with the homochiral aldehydes; N,N-dibenzyl valinal and N,N-dibenzyl leucinal. The diastereoselectivity is explained in terms of Masamune's model of double asymmetric induction using the concept of matched and mismatched pairs. The matched pair aldol product arising from the reaction with N,N-dibenzyl leucinal is converted into the known γ-amino-β-hydroxy acid, (3*R*,4*S*)-statine.

INTRODUCTION

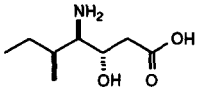
In 1970 a Japanese team isolated and characterised the pepsin inhibitor pepstatin.[1] The new peptide was isolated from the culture filtrates of various species of *actinomycetes* and shown to have the sequence:

isovaleryl-L-valyl-L-valyl-(3*S*,4*S*)-statyl-L-alanyl-(3*S*,4*S*)-statine.

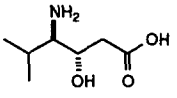
The constitution and absolute configuration of the novel amino acid component, statine **1**, was proved by both enantiospecific synthesis, from a sugar derivative,[2] and anomalous dispersion X-ray crystallography.[3]



(3*S*,4*S*)-Statine **1**



(3*S*,4*R*,5*S*)-Isostatine **2**



3

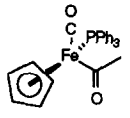
It was soon shown that pepstatin inhibited a number of other acid proteases *eg* renin and cathepsin D. Pepstatin, although an effective acid protease inhibitor, is not specific and so the search began for more selective analogues. The intense interest in this area developed due to the potential use of acid protease inhibitors in treatments for ulcers, inflammation and hypertension.[4] There has been a great deal of effort, in the pharmaceutical industry[5] and academia,[6] devoted to the synthesis and biological testing of derivatives of statine and its analogues. The biological activity of these analogues is found to depend strongly on the relative and absolute stereochemistry of the γ-amino-β-hydroxy acid functionality.[6b] Although the (3*S*,4*S*) stereochemistry found in nature is generally the most active, it is of use to be able to define this unambiguously for derivatives of particular interest, since this type of diastereomer comparison can help to define a structure-activity relationship.

Another series of natural products with potent biological activity, the didemnins, has been shown to contain the β-hydroxy-γ-amino acid functionality. Although there was an initially incorrect structure assignment,[7] didemnin B has now been shown[8] to contain (3*S*,4*R*,5*S*)-4-amino-3-hydroxy-5-methylheptanoic acid or isostatine, **2**.

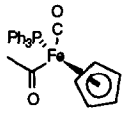
†Dedicated to Professor Sir Derek Barton, FRS on the occasion of his 75th birthday.

The cyclic depsipeptide, didemnin B, was the first marine natural product to enter clinical trials as a potential anticancer agent.[8a] A related β-hydroxy-γ-amino acid found in the didemnins is the valine derived compound **3**.[9]

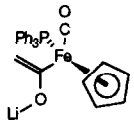
As has been previously described[10] the iron chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)] can control the stereochemical outcome of a wide range of reactions such as tandem Michael addition-alkylations[11] of attached α,β-unsaturated acyl ligands, and enolate alkylation and aldol reactions of acyl sidechains.[12] The iron acetyl complex [(η^5-C_5H_5)Fe(CO)(PPh_3)COMe] **4** , both enantiomers of which are readily available,[13] provides a chiral acetate enolate equivalent.



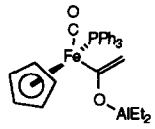
(*R*)-**4**



(*S*)-**4**

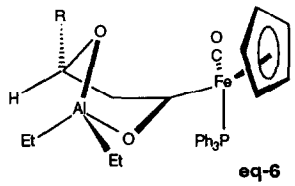


(*S*)-**5**

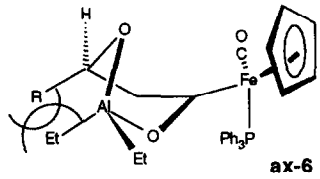


(*R*)-**6**

Although the lithium enolate **5** derived from **4** offers very little diastereoselectivity in reactions with prochiral aldehydes the derived diethyl aluminium enolate displays excellent and predictable diastereoselectivity in the aldol reaction. In all cases the diethyl aluminium enolate of **4** has been found to display the *R-Si/S-Re* diastereoselectivity, that is the aluminium enolate (*R*)-**6**, derived from (*R*)-**4**, attacks the *Si* face of an aldehyde in preference to its *Re* face.[11b,c] This selectivity has been rationalised in terms of a preferred boat transition state **eq-6** in which the aldehyde side chain avoids an unfavourable 1,3-diaxial interaction with the ethyl groups on the aluminium centre which would occur in the alternative boat transition state **ax-6**. The alternative chair transition states would both be destabilised by severe steric interactions between the cyclopentadienyl ring and one of the aluminium ethyl ligands.



eq-6

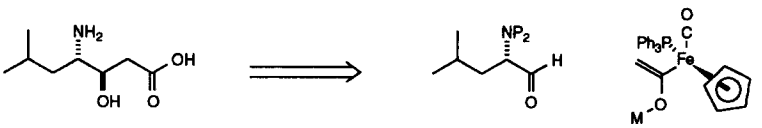


ax-6

The phrase "asymétrique par double induction", double asymmetric induction, was coined by Horeau, Kagan and Vigneron[14] in the late 60's. Since then papers on the subject have appeared sporadically[15] with Heathcock[16] introducing the alternative phrase "double stereodifferentiation". In 1985 Masamune used a wide range of examples to postulate the generality of the theory of double asymmetric induction and introduced the terms "matched pair" and "mismatched pair".[17]

There are a few examples in the literature of aldol reactions between iron acyl enolates and chiral aldehydes.[18] In these cases one would expect to see double asymmetric induction and the emergence of matched and mismatched pairs, as described by Masamune. This is indeed the case, although the asymmetric induction from the aldehyde is usually low and is largely overcome by the more powerful influence of the iron chiral auxiliary.

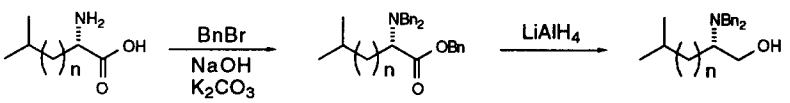
Many different strategies have been used to synthesise statine and generally they offer little diastereoselectivity. One of the most often repeated is an aldol reaction between an N-protected α-amino aldehyde and an achiral acetate enolate,[19] although a few chiral enolates[5b,d] have also been used. It was thought that through the use of the chiral iron acetyl reagent **4** a highly diastereoselective synthesis of (3*R*,4*S*)-statine could be realised, via an aldol reaction with an N-protected α-amino aldehyde.



Preliminary work indicated that the often used Boc protected α-amino aldehydes were not suitable for coupling to the iron acetyl enolate, due to competing deprotonation of the substrate, leading to low yields. Of the alternative protecting groups, the N,N-dibenzyl group, as advocated by Reetz,[20] appeared to be the most promising. This protecting group confers greater diastereofacial selectivity and improved configurational stability on α-amino aldehydes in comparison with the conventional Boc group. Reetz reported high levels of diastereoselectivity in nucleophilic additions to N,N-dibenzyl-α-amino aldehydes, by both Grignard reagents and lithium enolates.[21] The inherent non-chelation controlled facial selectivity of N,N-dibenzyl-α-amino aldehydes has been rationalised by the Felkin-Anh model.[22] Heathcock and Lodge have provided an excellent discussion[23] of the various models that have been proposed to explain diastereofacial selectivity for carbonyls bearing α-stereogenic centres.

RESULTS AND DISCUSSION

The N,N-dibenzylamino alcohols (*S*)-**7** and (*S*)-**8** were prepared from (*S*)-valine and (*S*)-leucine via the esters (*S*)-**9** and (*S*)-**10**, according to the method of Reetz[21] in overall yields of 43% and 82% respectively.

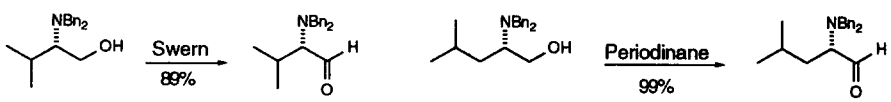


(*S*)-**9**, n=0
(*S*)-**10**, n=1

(*S*)-**7**, n=0, 43%
(*S*)-**8**, n=1, 82%

^{1}H nmr spectroscopic data were identical to those reported but the specific rotations for (*S*)-**7** and (*S*)-**8**: $[\alpha]_D^{20}$ +15.2 (c 2.60, CH_2Cl_2) [Lit: $[\alpha]_D^{20}$ +16.9 (c 2.67, CH_2Cl_2)] and $[\alpha]_D^{20}$ +75.9 (c 2.02, CH_2Cl_2) [Lit: $[\alpha]_D^{20}$ +83.9 (c 1.99, CH_2Cl_2)], were somewhat lower than reported[24]. This was a worrying discrepancy and therefore an alternative means of assessing the optical purity of one of the alcohols, (*S*)-**8**, was sought. A report[25] by Parker and Taylor suggested O-acetylmandelic acid to be a useful nmr chiral shift reagent for amino alcohols. In order to use this method the racemic alcohol (*RS*)-**8** first had to be prepared. This was carried out in an exactly analogous manner to the preparation of (*S*)-**8**, but using (*RS*)-leucine as the starting material and on a considerably smaller scale, to give (*RS*)-**8** in an overall yield of 49%.

Chiral shift studies were carried out in deuteriochloroform at 300 MHz and indicated that the alcohol (*S*)-**8** was indeed homochiral, within the limits of detection, in spite of polarimetric evidence suggesting it to be of only 90% ee. An enantiomeric excess of >98% was confidently assigned to this material.



(*S*)-**7** (*S*)-**11** (*S*)-**8** (*S*)-**12**

The alcohol (*S*)-**7** was oxidised using the Swern procedure[26] to give the aldehyde (*S*)-**11** in 89% yield. Subsequently, the Dess-Martin periodinane[27] was found to be a more convenient protocol and was used to oxidise (*S*)-**8** to the aldehyde (*S*)-**12** in essentially quantitative yield. The aldehydes were used immediately since attempts to store the aldehyde (*S*)-**12**, even at low temperature, were frustrated by its chemical lability; after two weeks at -30°C, ^{1}H nmr spectroscopic analysis of a sample showed almost none of the characteristic aldehydic peak at δ 9.78. It may be speculated that trimerisation is occurring, as is well documented for many other aldehydes *eg* formaldehyde and isopropylidene glyceraldehyde.[28]

Aldol Reactions

The orange iron acetyl complex (*RS*)-**4** was dissolved in THF and cooled to -70°C before being treated with butyllithium to generate the deep red lithium enolate (*RS*)-**5**. A THF solution of the freshly prepared aldehyde (*S*)-**11** (1.0 equivalent) was added to the enolate and the orange solution quenched with methanol after being allowed to stir for 1 hour. After an aqueous work-up and filtration of an ethyl acetate solution through a plug of deactivated alumina the crude reaction mixture was analysed by both ^{1}H and ^{31}P nmr spectroscopy at 300 and 101 MHz respectively. The ^{31}P nmr spectrum showed a peak for each of the four possible diastereomeric products together with a small amount of returned starting complex **4**. The ratio of products is shown in Table 1 together with the stereochemical assignments which were made with the help of later experiments (the first configurational descriptor refers to the stereogenic centre at iron, the next to the hydroxyl bearing stereogenic centre and the third to the amino bearing stereogenic centre). The crude product was purified by silica gel chromatography (SGC) to give, in 88% yield, a mixture of all four diastereomers **13-16**, which were characterised by elemental analysis and mass spectrometry.

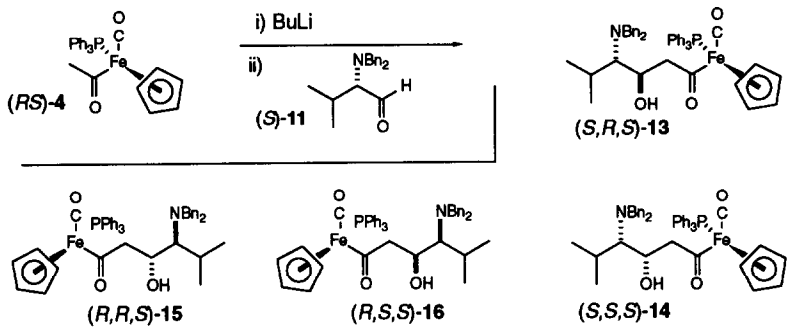


Table 1: Product Ratios of Aldol Reactions with (*S*)-**11**

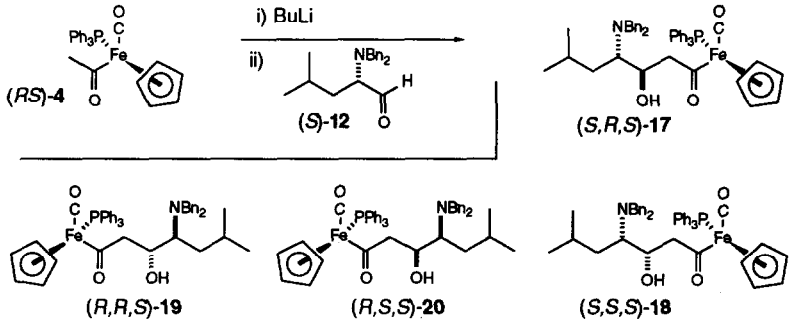
Enolate	(*S,R,S*)-**13**	(*S,S,S*)-**14**	**4**	(*R,R,S*)-**15**	(*R,S,S*)-**16**
(*RS*)-**5**	8.9	6.0	1.0	8.3	5.0
(*R*)-**6**	-	-	4.2	1.0	4.0
(*S*)-**6**	23.0	1.0	21.2	-	-

In an identical manner to the above, the homochiral enolate (*R*)-**5** was generated but then treated with an excess of diethylaluminium chloride and warmed to -40°C for 2 hours in order to allow transmetallation to occur. The thus formed aluminium enolate (*R*)-**6** was cooled to -100°C and a THF solution of the aldehyde (*S*)-**11** was added. After 5 hours the reaction was quenched and subjected to an aqueous work-up before analysis of the product distribution by both ^{1}H and ^{31}P nmr spectroscopy. The ^{31}P nmr spectrum showed a mixture of diastereomers **15** and **16** together with unreacted starting material (*R*)-**4**, (see Table 1). Also present was a small amount of the diastereomer (*R,S,R*)-**13** presumably arising from a small amount of the enantiomeric aldehyde (*R*)-**11**. Purification by SGC allowed the aldol products to be isolated in 48% yield. Under identical conditions the homochiral aluminium enolate (*S*)-**6** was generated and allowed to react with the aldehyde (*S*)-**11**, (see

Table 1). The aldol products **13** and **14** were isolated by SGC in 44% yield and fully characterised for the major product **13**.

From the reactions described above it is clear that the aldehyde (*S*)-**11** reacts with the aluminium enolate (*S*)-**6** in a matched pair reaction to give the aldol products (*S,R,S*)-**13** and (*S,S,S*)-**14** in a ratio of 23:1. When the enantiomeric enolate, (*R*)-**6**, is allowed to react with (*S*)-**11** the products (*R,S,S*)-**16** and (*R,R,S*)-**15** are formed, with a ratio of 4:1, in a mismatched pair reaction. In this example it can be seen that the aldehyde is exerting the expected Felkin-Anh facial selectivity. Although the diastereoselectivity in the mismatched pair reaction is considerably reduced, in comparison with the matched pair, the iron auxiliary still determines the major product of the reaction.

It was expected that the homologous aldehyde (*S*)-**12** would behave in a very similar manner to (*S*)-**11** and as before in order to determine the distinguishing nmr characteristics of all of the possible diastereomers in the aldol reaction between (*S*)-**12** and complex **4** the lithium enolate was utilised since this is known to be non-stereoselective.



In an exactly analogous reaction to that described above the lithium enolate derived from (*RS*)-**4** was treated with the aldehyde (*S*)-**12**. After work-up the crude mixture was analysed by both ^{1}H and ^{31}P nmr spectroscopy at 300 and 101 MHz respectively. As before the proton spectrum was extremely complex and the only useful feature was the group of resolved resonances due to the cyclopentadienyl protons. Five singlets (or fine doublets, J 1.2) were observed and these were assigned (with the help of later evidence - see below) as shown in Table 2.

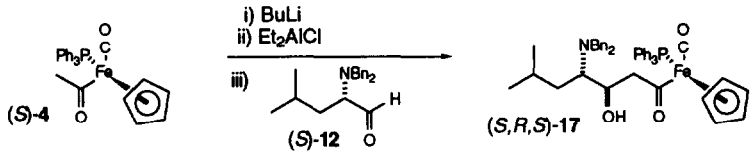
Table 2: Product Ratios of Aldol Reactions with (*S*)-**12**

Enolate	(*S,R,S*)-**17**	(*S,S,S*)-**18**	**4**	(*R,R,S*)-**19**	(*R,S,S*)-**20**
(*RS*)-**5**	3.2	1.0	3.6	2.8	1.3
(*RS*)-**6**	5.0	-	3.8	1.0	4.3
(*S*)-**6**	25.0	1.0	10.6	-	-

It is apparent from these data that the aldehyde is showing the expected *Re* diastereofacial preference, *Re*:*Si* = 2.6:1, while the lithium enolate shows a very slight (1.2:1) *R-Si*/*S-Re* facial selectivity.

So as to be more confident of the assignments made, it was necessary to reduce the number of diastereomers produced in the aldol reaction and this was achieved by transmetallating the lithium enolate to the aluminium enolate (*RS*)-**6**. The reaction was carried out in the same manner as for the lithium enolate except that diethyl aluminium chloride was added to (*RS*)-**5** and the solution equilibrated at -40°C for 45 minutes to effect complete transmetallation. The crude product mixture was analysed in the same way as before and the results are shown in Table 2. Clearly the enolate has now been endowed with diastereofacial selectivity. Only the major diastereomer (*S,R,S*)-**17** of the matched pair reaction is now discernible; in the mismatched pair [(*R*)-**6** + (*S*)-**12**] the (*R,S,S*)-**20** diastereomer, that favoured by the iron auxiliary, predominates.

Having completed the necessary control experiments it was possible to proceed with the matched pair reaction using homochiral (*S*)-**4** to generate the diethyl aluminium enolate (*S*)-**6**.

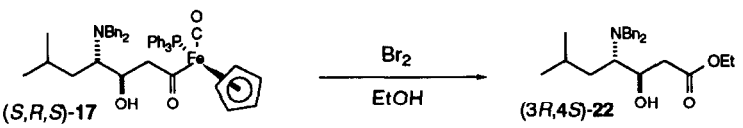


The reaction was carried out and the crude product analysed in the same manner as before; the product ratio is shown in Table 2. The matched pair reaction between the homochiral iron acetyl enolate (*S*)-**6** and the homochiral α-amino aldehyde (*S*)-**12** proceeded with very good diastereoselectivity, as predicted, to give (*S,R,S*)-**17**.

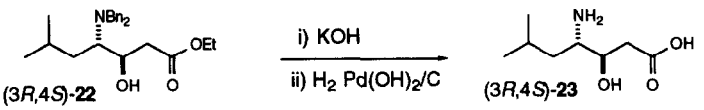
The crude product was purified by SGC to give a 71% yield of (*S,R,S*)-**17** which was fully characterised, including elemental micro-analysis.

Decomplexation and Deprotection to give (3R,4S)-Statine

A cooled solution of (*S,R,S*)-**17** in ethanol/CH_2Cl_2 was treated with bromine which immediately turned the yellow solution to a deep green colour. After an aqueous work-up and purification by SGC the green complex [(η^5-C_5H_5)Fe(CO)(PPh_3)Br] **21** was isolated in quantitative yield, as well as the desired product (3*R*,4*S*)-ethyl dibenzyl statine **22** which was isolated in 65% yield.



Although **22** has been described in the literature[21] no physical or spectroscopic data was presented, therefore this material was fully characterised, including elemental micro-analysis.



In order to effect complete deprotection and synthesis of free statine **23**, the ester **22** was saponified with aqueous potassium hydroxide and the N,N-dibenzyl groups were removed by hydrogenolysis over Pearlman's catalyst. The acetate salt was finally purified by ion exchange chromatography to give (3*R*,4*S*)-statine **23** as a white solid in 64% yield. The melting point of 200°C (dec.) compared favourably with the literature value:[2] mp 202-203°C (dec.), while the ^{1}H nmr and mass spectra were both entirely consistent with the structure of statine. Furthermore a commercial sample of the diastereomeric (3*S*,4*S*)-statine was acquired, and its 500 MHz ^{1}H nmr spectrum compared with that of **23** at the same frequency: the spectra were clearly different but each contained the same groups of resonances, with correct integrations, at similar chemical shifts.

CONCLUSION

This work has further demonstrated the fact that the iron acetyl complex **4** is capable of providing a highly diastereoselective acetate enolate equivalent. The complex has been used to synthesise the unusual β-hydroxy-γ-amino acid, (3*R*,4*S*)-statine **23**, incorporating as the key step, an aldol reaction under double asymmetric control.

EXPERIMENTAL

General

All manipulations of organometallic complexes were performed under an atmosphere of nitrogen with deoxygenated solvents and using standard vacuum line and Schlenk tube techniques.[29] Butyllithium was used as a 1.6M solution in hexanes and diethylaluminium chloride as a 2.0M solution in toluene. Dimethylsulfoxide (DMSO) was dried over 4Å molecular sieves prior to use. THF was dried over sodium benzophenone ketyl and distilled.

Melting points were determined using a Gallenkamp apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Dyson Perrins analytical department. Infra-red spectra were recorded in 0.1 mm solution cells on a Perkin-Elmer 781 spectrophotometer. ^{1}H nmr spectra were recorded on Bruker WH300 and AM500 spectrometers whereas ^{13}C and ^{31}P nmr spectra were recorded on a Bruker AM250 instrument. Spectra were recorded in $CDCl_3$ solution at ambient temperature unless otherwise stated. Mass spectra for organometallic complexes were obtained on a V.G. Micromass ZAB1F instrument using fast atom bombardment ionisation techniques whilst those for organic compounds were obtained on the same instrument using chemical ionisation methods.

(*S*)-2-(N,N-Dibenzylamino)-3-methylbutanol (*S*)-7

To a solution of NaOH (4.30 g, 107 mmol) and K_2CO_3 (14.5 g, 107 mmol) in water (100 ml), was added (*S*)-(+)-valine (6.27 g, 53.6 mmol) and the mixture heated to reflux. Benzyl bromide (19.2 ml, 162 mmol) was added dropwise and heating continued for 30 min before cooling in an ice bath. The mixture was extracted with ether (3 x 50 ml), dried and the solvent evaporated to give a pale yellow oil (20.2 g). The oil was redissolved in dry ether (70 ml) and added to a cooled (0°C) suspension of $LiAlH_4$ (6.4 g, 168 mmol) in ether (100 ml). The mixture was allowed to warm to 20°C and stirred for 4h before being cooled (0°C) and cautiously treated with water (3.5 ml), aq. NaOH (3.5 ml, 4 M) and water (10 ml), the solids were filtered and washed with ether (4 x 50 ml). After concentration of the combined filtrates, the benzyl alcohol was removed by distillation (bp 46°C/0.1mmHg) and, the residue purified by SGC (petrol/ether) to give the title compound as a pale yellow oil (13.0 g, 46.0 mmol, 43%).$[\alpha]_D^{20}$ +15.2 (c 2.60, CH_2Cl_2) [Lit:[24] $[\alpha]_D^{20}$ +16.9 (c 2.67, CH_2Cl_2)]; δ_H 0.88, 1.13 (6H, 2d, J 6.7, CH*Me*$_2$), 2.05 (1H, m, C*H*Me$_2$), 2.53 (1H, m, C*H*N), 2.98 (1H, br s, O*H*), 3.43-3.55 (2H, m, C*H*$_2$OH), 3.68, 3.88 [4H, AB system, J_{AB} 13.2, N(C*H*$_2$Ph)$_2$], 7.23-7.37 (10H, m, *Ph*).

(*S*)-2-(N,N-Dibenzylamino)-4-methylpentanol (*S*)-8

In an identical manner (*S*)-(+)-leucine (5.00 g, 38.0 mmol) was treated with NaOH (3.00 g, 76.0 mmol), K_2CO_3 (10.5 g, 76.0 mmol) and benzyl bromide (13.7 ml, 115 mmol) followed by $LiAlH_4$ (3.5 g, 92 mmol) to give the title compound as a pale yellow oil (9.24 g, 31.1 mmol, 82%).$[\alpha]_D^{20}$ +75.9 (c 2.02, CH_2Cl_2) [Lit:[24] $[\alpha]_D^{20}$ +83.9 (c 1.99, CH_2Cl_2)]; δ_H 0.86, 0.93 (6H, 2d, J 6.1, CH*Me*$_2$), 1.13-1.57 (3H, m, C*HCH*$_2$), 2.85 (1H, m, C*H*N), 3.24 (1H, br s, O*H*), 3.41 (2H, m, C*H*$_2$OH), 3.37, 3.81 [4H, AB system, J_{AB} 13.2, N(C*H*$_2$Ph)$_2$], 7.21-7.34 (10H, m, *Ph*). Chiral shift study: the racemic alcohol (*RS*)-**8** (4.9 mg, 0.016 mmol) was dissolved in $CDCl_3$ (0.4 ml), treated with (*R*)-(-)-O-acetylmandelic acid (4.0 mg, 0.021 mmol, 1.3 eq.) and the ^{1}H nmr spectrum recorded at 300 MHz. Comparison with the spectrum obtained from the pure alcohol (*RS*)-**8**, in $CDCl_3$ at the same frequency, showed a number of changes including increased splitting of two of the

multiplets: a three proton doublet at δ 0.86 became two doublets at δ 0.78, 0.79. Of greater interest was the excellent baseline resolution achieved at lower field. The four benzylic protons form an AB system at δ 3.37, 3.81 which was further split into two AB systems at δ 3.52, 4.07 and δ 3.52, 4.12, by the chiral shift reagent. The alcohol (*S*)-**8** was treated in an analogous manner with (*R*)-(-)-O-acetylmandelic acid and the ^{1}H nmr spectrum recorded at 300 MHz. The spectrum showed only a single doublet at δ 0.77 and a single benzylic AB system at δ 3.54, 4.15, expansion of the relevant portion of the spectrum failed to show any peaks that could be assigned to the (*R*) enantiomer of **8**. Thus in spite of polarimetric evidence suggesting the alcohol (*S*)-**8** to be of only 90% ee, an independent assay proved that the alcohol was indeed homochiral, within the limits of detection. An enantiomeric excess of >98% was confidently assigned to this material.

(*S*)-2-(N,N-Dibenzylamino)-3-methylbutanal (*S*)-11

Oxalyl chloride (1.0 ml, 11.5 mmol) was added to a cooled (-70°C) solution of CH_2Cl_2 (30 ml) followed by dropwise addition of DMSO (1.4 ml, 19.9 mmol) in CH_2Cl_2 (3 ml). The solution was stirred for 3 min before addition of (*S*)-2-(N,N-dibenzylamino)-3-methylbutanol (2.69 g, 9.47 mmol) as a solution in CH_2Cl_2 (20 ml). After stirring for 45 min triethylamine (5.3 ml, 38 mmol) was added to the reaction and the mixture allowed to warm to 20°C. Water (50 ml) was added and the mixture extracted with CH_2Cl_2 (3 x 20 ml); the combined organic extracts were washed with aq. HCl (1%, 10 ml), water (20 ml), aq. Na_2CO_3 (5%, 20 ml) and brine (20 ml) and dried over Na_2SO_4. Evaporation of the solvent gave the crude product which was purified by SGC (CH_2Cl_2) to give the title compound as a pale yellow oil (2.37 g, 8.43 mmol, 89%); δ_H 0.88, 1.09 (6H, 2d, J 6.6, CH*Me*$_2$), 2.29 (1H, m, C*H*Me$_2$), 2.73 (1H, dd J 10.0, 3.4, C*H*N), 3.72, 4.03 [4H, AB system, J_{AB} 13.8, N(C*H*$_2$Ph)$_2$], 7.21-7.40 (10H, m, *Ph*), 9.86 (1H, d, J 3.4, C*H*O).

(*S*)-2-(N,N-Dibenzylamino)-4-methylpentanal (*S*)-12

To a stirred solution of (*S*)-2-(N,N-dibenzylamino)-4-methylpentanol (205 mg, 0.69 mmol) in CH_2Cl_2 (10 ml) was added solid periodinane (382 mg, 0.90 mmol), after 30 min at 20°C the reaction was diluted with ether (80 ml) and quenched with aq. NaOH (0.5 M, 30 ml). The mixture was stirred for 15 min, separated and the ether layer re-extracted with aq. NaOH (0.5 M, 15 ml) before drying and, evaporation of the solvent to give a yellow oil. This was further dried by azeotroping with toluene (2 x 5 ml) to give the title compound (202 mg, 0.68 mmol, 99%). This material was used immediately in the following reaction; δ_H 0.79, 0.84 (6H, 2d, J 6.3, CH*Me*$_2$), 1.45-1.71 (3H, m, C*HCH*$_2$), 3.24 (1H, t, J 6.3, C*H*N), 3.71, 3.79 [4H, AB system, J_{AB} 13.2, N(C*H*$_2$Ph)$_2$], 7.23-7.42 (10H, m, *Ph*), 9.78 (1H, s, C*H*O).

(*S*,*R*,*S*)-, (*S*,*S*,*S*)-, (*R*,*R*,*S*)-, (*R*,*S*,*S*)-[(η^5-C_5H_5)Fe(CO)(PPh$_3$)COCH$_2$CH(OH)CH(NBn$_2$)CHMe$_2$] 13, 14, 15, 16.

To a cooled (-70°C) solution of (*RS*)-[(η^5-C_5H_5)Fe(CO)(PPh$_3$)COMe] (200 mg, 0.44 mmol) in THF (10 ml) was added BuLi (0.33 ml, 0.53 mmol) and the deep red enolate solution stirred for 30 min before addition of (*S*)-2-(N,N-dibenzylamino)-3-methylbutanal (124 mg, 0.44 mmol), as a solution in THF (4 ml). After 1h the reaction was quenched with methanol (2 ml), warmed to 20°C and the solvents evaporated. The residue was triturated with CH_2Cl_2 and the combined extracts washed sequentially with: aq. HCl (5%, 2 x 10 ml), water (3 x 10 ml) and sat. aq. $NaHCO_3$ (2 x 10 ml). The organic layer was filtered through a short plug of deactivated alumina (eluting with ethyl acetate) and the solvent evaporated to give a crude orange foam. ^{1}H and ^{31}P nmr analysis of the mixture revealed all four of the product diastereomers together with recovered starting material. From the ^{1}H nmr only the chemical shifts due to the cyclopentadienyl protons are listed, together with the stereochemical assignments made. The crude product was purified by chromatography (alumina eluting with ether) to give recovered starting complex **4** (9 mg) together with a mixture of all four diastereomers of the product **13**, **14**, **15** and **16** as an orange foam (287 mg, 0.39 mmol, 88%), (Found: C, 73.48; H, 6.35; N, 2.01.

$C_{45}H_{46}FeNO_3P$ requires C, 73.46; H, 6.31; N, 1.90%); δ_H 4.33 (*S,S,S*), 4.39 (*S,R,S*), 4.43 (*R,R,S*), 4.45 (*R,S,S*); δ_P (101.2 MHz; solvent $CDCl_3$; standard trimethylphosphite) 72.56 (*R,S,S*), 72.65 (*R,R,S*), 72.88 (SM), 73.37 (*S,S,S*), 73.39 (*S,R,S*); m/z (FAB) 736 (M^+), 91 ($C_7H_7^+$).

(*R,R,S*)-, (*R,S,S*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OH)CH(NBn_2)CHMe_2$] 15, 16.

To a cooled (-70°C) solution of (*R*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COMe] (200 mg, 0.44 mmol) in THF (10 ml) was added BuLi (0.33 ml, 0.53 mmol) and the deep red enolate solution stirred for 30 min before addition of a toluene solution of diethylaluminium chloride (1.3 ml, 2.6 mmol). The solution was warmed to -40°C for 2h and then cooled to -100°C before addition of (*S*)-2-(N,N-dibenzylamino)-3-methylbutanal (124 mg, 0.44 mmol), as a solution in THF (4 ml). After 5h the reaction was quenched and worked-up as above. ^1H and ^{31}P nmr analysis of the mixture revealed three of the product diastereomers together with recovered starting material. The crude product was purified by chromatography (alumina eluting with ether) to give recovered starting complex **4** (79 mg) together with a mixture of three diastereomers of the product (*R,S,R*)-**13**, **15** and **16** as an orange foam (155 mg, 0.21 mmol, 48%). Major diastereomer **16**: ν_{max} (CH_2Cl_2)/cm^{-1} 3400br (OH), 1916vs (FeCO), 1602s (FeCOR), δ_H 0.96, 0.99 (6H, 2d, J 6.6, CH*Me*$_2$), 2.06 (2H, m, C*H*C*H*Me$_2$), 2.68, 3.26 (2H, ABX system, J_{AB} 16.8, J_{AX} 0, J_{BX} 10.2, COC*H*$_2$), 3.63 (1H, s, O*H*), 3.66 (1H, m, C*H*OH), 3.63, 3.97 [4H, AB system, J_{AB} 13.4, N(C*H*$_2$Ph)$_2$], 4.45 (5H, d, J 1.2, *Cp*), 7.15-7.51 (25H, m, *Ph*), δ_C 20.8, 22.4 (CH*Me*$_2$), 27.2 (*C*HMe$_2$), 55.7 [N(*C*H$_2$Ph)$_2$], 66.0, 68.1 (*C*HOH, *C*HN), 71.6 (CO*C*H$_2$), 85.3 (*Cp*), 126.6-141.6 (*Ph*), 204.4 (Fe*C*OR), 220.3 (Fe*C*O).

(*S,R,S*)-, (*S,S,S*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OH)CH(NBn_2)CHMe_2$] 13, 14.

In an identical manner to that above the diethylaluminium enolate derived from (*S*)-**4** was reacted with (*S*)-**11** to give a mixture of diastereomers **13** and **14** (144 mg, 0.20 mmol, 44%) together with unreacted starting material **4** (90 mg). Major diastereomer **13**: ν_{max} (CH_2Cl_2)/cm^{-1} 3450br (OH), 1917vs (FeCO), 1585s (FeCOR), δ_H 0.94, 0.97 (6H, 2d, J 6.6, CH*Me*$_2$), 1.61 (1H, m, C*H*Me$_2$), 2.10 (1H, m, C*H*N), 2.97, 3.27 (2H, ABX system, J_{AB} 18.7, J_{AX} 9.9, J_{BX} 0, COC*H*$_2$), 3.27 (1H, d, J 2.6, O*H*), 3.53, 3.57 [4H, AB system, J_{AB} 13.9, N(C*H*$_2$Ph)$_2$], 3.95 (1H, m, C*H*OH), 4.39 (5H, d, J 1.2, *Cp*), 7.19-7.55 (25H, m, *Ph*), δ_C 19.8, 23.3 (CH*Me*$_2$), 25.6 (*C*HMe$_2$), 54.5 [N(*C*H$_2$Ph)$_2$], 64.7, 66.5 (*C*HOH, *C*HN), 72.5 (CO*C*H$_2$), 85.3 (*Cp*), 126.9-140.6 (*Ph*), 204.4 (Fe*C*OR), 220.3 (Fe*C*O).

(*S,R,S*)-, (*S,S,S*)-, (*R,R,S*)-, (*R,S,S*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OH)CH(NBn_2)CH_2CH$-Me$_2$] 17, 18, 19, 20.

In an analogous manner to that described above, the lithium enolate derived from (*RS*)-**4** (100 mg, 0.22 mmol) was reacted with (*S*)-2-(N,N-dibenzylamino)-4-methylpentanal (71 mg, 0.24 mmol). ^1H and ^{31}P nmr analysis of the crude product mixture revealed all four of the product diastereomers together with recovered starting material. From the ^1H nmr only the chemical shifts due to the cyclopentadienyl protons are listed, together with the relative intensities and stereochemical assignments made: δ_H 4.37 (1.0, *S,S,S*), 4.40 (3.2, *S,R,S*), 4.43 (3.6, SM), 4.44 (2.8, *R,R,S*), 4.46 (1.3, *R,S,S*); δ_P (101.2 MHz; solvent $CDCl_3$; standard trimethylphosphite) 72.05 (*R,S,S*), 72.33 (*R,R,S*), 72.82 (*S,S,S*), 72.92 (SM), 73.00 (*S,R,S*).

(*S,R,S*)-, (*R,R,S*)-, (*R,S,S*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OH)CH(NBn_2)CH_2CHMe_2$] 17, 19, 20.

To a cooled (-70°C) solution of (*RS*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COMe] (100 mg, 0.22 mmol) in THF (5 ml) was added BuLi (0.26 ml, 0.44 mmol) and the deep red enolate solution stirred for 30 min before addition of diethylaluminium chloride (0.55 ml, 1.1 mmol). The solution was warmed to -40°C for 45 min, recooled to

-70°C, and (*S*)-2-(N,N-dibenzylamino)-4-methylpentanal (89 mg, 0.30 mmol), as a solution in toluene (5 ml), was added dropwise. After 3h the reaction was quenched with methanol (1 ml), warmed to 20°C and the solvent evaporated. The residue was triturated with $CHCl_3$, filtered through a short plug of deactivated alumina and the solvent evaporated to give a crude orange foam.In an analogous manner to that described above, the diethylaluminium enolate derived from (*RS*)-**4** (100 mg, 0.22 mmol) was reacted with (*S*)-2-(N,N-dibenzylamino)-4-methylpentanal (89 mg, 0.30 mmol). ^1H and ^{31}P nmr analysis of the mixture revealed three of the product diastereomers together with recovered starting material. From the ^1H nmr only the chemical shifts due to the cyclopentadienyl protons are listed, together with the relative intensities and stereochemical assignments made: δ_H 4.40 (5.0, *S,R,S*), 4.43 (3.8, SM), 4.44 (1.0, *R,R,S*), 4.46 (4.3, *R,S,S*); δ_P (101.2 MHz; solvent $CDCl_3$; standard trimethylphosphite) 72.05 (*R,S,S*), 72.33 (*R,R,S*), 72.92 (SM), 73.00 (*S,R,S*).

(*S,R,S*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OH)CH(NBn_2)CH_2CHMe_2$] 17

To a cooled (-70°C) solution of (*S*)-(+)-[(η^5-C_5H_5)Fe(CO)(PPh_3)COMe] (245 mg, 0.54 mmol) in THF (5 ml) was added BuLi (0.74 ml, 1.19 mmol) and the deep red enolate solution stirred for 1h before addition of diethylaluminium chloride (1.4 ml, 2.7 mmol). The solution was stirred for 2.5h at -70°C, warmed to -40°C for 15 min and, recooled to -70°C, at this point (*S*)-2-(N,N-dibenzylamino)-4-methylpentanal (200 mg, 0.68 mmol), as a solution in toluene (5 ml), was added dropwise and the reaction stirred for 6h. The reaction was quenched with methanol (2 ml), warmed to 20°C and diluted with ethyl acetate (30 ml). The organic layer was extracted with aq. HCl (1.6 M, 20 ml) and aq. NaOH (1.5 M, 50 ml), dried, filtered through a short plug of deactivated alumina and the solvent evaporated to give an orange foam. The product was purified by SGC (hexane/ethyl acetate, 7:1, R_f: 0.36) to give the title compound as an orange foam (288 mg, 0.38 mmol, 71%), $[\alpha]_D^{20}$ +29.3 (c 1.30, $CHCl_3$), (Found: C, 70.04; H, 6.48; N, 1.87. $C_{46}H_{48}FeNO_3P.HCl$ requires C, 70.27; H, 6.29; N, 1.78%), ν_{max} (CH_2Cl_2)/cm^{-1} 3410br (OH), 1915vs (FeCO), 1580s (FeCOR); δ_H 0.59, 0.86 (6H, 2d, J 6.6, CH*Me*$_2$), 1.01-1.58 (2H, m, CHC*H*$_2$), 1.82 (1H, hept, J 6.6, C*H*Me$_2$), 2.23 (1H, m, C*H*N), 2.79, 3.18 (2H, ABX system, J_{AB} 17.2, J_{AX} 10.7, J_{BX} 0, CO*CH*$_2$), 3.29 (1H, d, J 1.9, O*H*), 3.42, 3.65 [4H, AB system, J_{AB} 13.8, (*CH*$_2$Ph)$_2$], 3.83 (1H, dd, J 4.4, 10.6, C*H*OH), 4.40 (5H, d, J 1.2, *Cp*), 7.18-7.54 (25H, m, *Ph*); δ_C 22.3, 23.6 (CH*Me*$_2$), 24.9 (*C*HMe$_2$), 35.9 (CHCH$_2$), 54.3 ((*CH*$_2$Ph)$_2$), 58.1 (*C*HN), 67.9 (*C*HOH), 71.3 (CO*CH*$_2$), 85.2 (*Cp*), 126.6-140.8 (*Ph*), 220.4 (Fe*C*OR), 283.5 (Fe*C*O); δ_P (101.2 MHz; solvent $CDCl_3$; standard trimethylphosphite) 73.00; m/z (FAB) 750 (MH^+, 15%), 439 (25), 383 (55), 91 (100).

(3*R*,4*S*)-Ethyl N,N-dibenzylstatine (3*R*,4*S*)-22

To a cooled (-70°C) solution of (*S,R,S*)-**17** (150 mg, 0.20 mmol), in a mixture of ethanol (4 ml) and CH_2Cl_2 (4 ml), was added a CH_2Cl_2 solution of bromine (0.51 ml, 0.24 mmol). The yellow solution immediately turned deep green and was stirred for 15 min before quenching with sat. aq. $NaHCO_3$ (6 ml) and, warming to 20°C. The mixture was extracted with CH_2Cl_2 (3 x 15 ml), dried, and the solvent evaporated to give a green oil. The product was purified by SGC (1% ethanol/CH_2Cl_2) to give [(η^5-C_5H_5)Fe(CO)(PPh_3)Br] (100 mg, 0.20 mmol), as a green solid, and the title compound as a clear oil (50 mg, 0.13 mmol, 65%), $[\alpha]_D^{20}$ -5.2 (c 0.94, $CHCl_3$), (Found: C, 75.14; H, 8.61; N, 3.95. $C_{24}H_{33}NO_3$ requires C, 75.16; H, 8.67; N, 3.65%), ν_{max} ($CHBr_3$)/cm^{-1} 3490br (OH), 1717s (CO_2Et); δ_H 0.74, 0.93 (6H, 2d, J 6.5, CH*Me*$_2$), 1.27 (3H, t, J 7.1, CO_2CH_2*Me*), 1.62-1.71 (2H, m, CHC*H*$_2$), 1.88 (1H, heptet, J 6.5, C*H*Me$_2$), 2.41, 2.58 (2H, ABX system, J_{AB} 16.3, J_{AX} 9.7, J_{BX} 2.9, C*H*$_2$CO$_2$), 2.62 (1H, obscured m, C*H*N), 3.03 (1H, br s, O*H*), 3.63, 3.71 [4H, AB system, J_{AB} 13.7, (*CH*$_2$Ph)$_2$], 4.14 (2H, q, J 7.1, CO$_2$C*H*$_2$Me), 4.27 (1H, m, C*H*OH), 7.16-7.34 (10H, m, *Ph*); δ_C 14.1 (CO_2CH_2*Me*), 22.6, 23.2 (CH*Me*$_2$), 25.2 (*C*HMe$_2$), 35.3 (CHCH$_2$), 39.5 (*CH*$_2$CO$_2$), 54.6 [(*CH*$_2$Ph)$_2$] 58.2 (*C*HN), 68.0 (*C*HOH), 126.9, 128.2, 128.9 (*o-, m-, p-Ph*), 140.0 (*i-Ph*), 173.1 (*C*O$_2$Et); m/z 384 (MH^+, 100%), 266 (85)

(3*R*,4*S*)-Statine (3*R*,4*S*)-23

Ethyl (3*R*,4*S*)-N,N-dibenzylstatine **22** (38 mg, 0.098 mmol) was added to a solution of KOH (6 mg, 0.1 mmol) in THF (40 ml) and water (10 ml), the mixture was heated at reflux for 6h, cooled and the solvent evaporated to leave a pale brown oil. The residue was dissolved in 50% aq. acetic acid (4 ml), to which was added Pearlman's catalyst (40 mg), and the mixture was stirred for 4h at 80°C under an atmosphere of hydrogen (4 atm.). The cooled solution was filtered through celite and the solvent evaporated to give a white solid, which was dissolved in the minimum of aq. HCl (1 M) and evaporated to dryness. The salt was dissolved in water (1 ml) and applied to an ion exchange column (Dowex 50X8-100, acid form), this was washed with water (200 ml) and then the product eluted with aq. NH_3 (1 M, 250 ml). Freeze-drying of the basic fractions gave (3*R*,4*S*)-statine as a fluffy white solid (11 mg, 0.063 mmol, 64%). Recrystallisation of a sample from ethanol/water gave a crystalline solid mp 200°C (dec.), [Lit.[2] mp 202-203°C (dec.)]; δ_H (D_2O) 0.75, 0.80 (6H, 2d, J 6.5, $CHMe_2$), 1.23-1.55 (3H, m, $CHCH_2$), 2.22, 2.28 (2H, ABX system, J_{AB} 15.1, J_{AX} 7.9, J_{BX} 5.7, CH_2CO_2), 3.26 (1H, m, CHN), 4.08 (1H, m, CHOH); m/z 176 (MH^+, 100%), 158 (35), 86 (65).

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REFERENCES

1 (a) H. Umezawa, T. Aoyagi, H. Morishima, M. Matsuzaki, M. Hamada, T. Takeuchi, *J. Antibiotics*, **1970**, *23*, 259. See also: (b) T. Miyano, M. Tomiyasu, H. Iizuka, S. Tomisaka, T. Takita, T. Aoyagi, H. Umezawa, *J. Antibiotics*, **1972**, *25*, 489; (c) H. Morishima, T. Takita, H. Umezawa, *J. Antibiotics*, **1973**, *26*, 115.

2 M. Kinoshita, S. Aburaki, A. Hagiwara, J. Imai, *J. Antibiotics*, **1973**, *26*, 249.

3 H. Nakamura, H. Morishima, T. Takita, H. Umezawa, Y. Iitaka, *J. Antibiotics*, **1973**, *26*, 255.

4 T. Aoyagi, H. Umezawa, *Cold Spring Harbor Conf. Cell Proliferation*, **1975**, *2*, 429.

5 (a) K.E. Rittle, C.F. Homnick, G.S. Ponticello, B.E. Evans, *J. Org. Chem.*, **1982**, *47*, 3016; (b) P.W.K. Woo, *Tetrahedron Lett.*, **1985**, *26*, 2973; (c) R.M. Devant, H.-E. Radunz, *Tetrahedron Lett.*, **1988**, *29*, 2307; (d) P.G.M. Wuts, S.R. Putt, *Synthesis*, **1989**, 951; (e) H. Yanagisawa, T. Kanazaki, T. Nishi, *Chemistry Lett.*, **1989**, 687.

6 (a) D.H. Rich, E.T. Sun, A.S. Boparai, *J. Org. Chem.*, **1978**, *43*, 3624; (b) W.-S. Liu, S.C. Smith, G.I. Glover, *J. Med. Chem.*, **1979**, *22*, 577; (c) S. Danishefsky, S. Kobayashi, J.F. Kerwin Jr., *J. Org. Chem.*, **1982**, *47*, 1981; (d) Y. Takemoto, T. Matsumoto, Y. Ito, S. Terashima, *Tetrahedron Lett.*, **1990**, *31*, 217; (e) J.V.N.V. Prasad, D.H. Rich, *Tetrahedron Lett.*, **1990**, *31*, 1803; (e) M. Bessodes, M. Saiah, K. Antonakis, *J. Org. Chem.*, **1992**, *57*, 4441.

7 K.L. Rinehart Jr., J.B. Gloer, J.C. Cook Jr., *J. Am. Chem. Soc.*, **1981**, *102*, 1857.

8 (a) K.L. Rinehart, V. Kishore, S. Nagarajan, R.J. Lake, J.B. Gloer, F.A. Bozich, K.-M. Li, R.E. Maleczka Jr., W.L. Todsen, M.H.G. Munro, D.W. Sullins, R. Sakai, *J. Am. Chem. Soc.*, **1987**, *109*, 6846; (b) B.D. Harris, M.M. Joullie, *Tetrahedron*, **1988**, *44*, 3489; (c) P. Jouin, J. Poncet, M.-N. Dufour, A. Pantaloni, B. Castro, *J. Org. Chem.*, **1989**, *54*, 617; (d) Y. Hamada, Y. Kondo, M. Shibata, T.Shioiri,*J. Am. Chem. Soc.*, **1989**, *111*, 669.

9 I. Maugras, J. Poncet, P. Jouin, *Tetrahedron*, **1990**, *46*, 2807.

10 S.G. Davies, *Aldrichimica Acta*, **1990**, *23*, 31.

11 (a) N. Aktogu, H. Felkin, S.G. Davies, *J. Chem. Soc., Chem. Commun.*, **1982**, 1303; (b) S.G. Davies, I.M. Dordor, P. Warner, *J. Chem. Soc., Chem. Commun.*, **1984**, 956; (c) S.G. Davies, I.M. Dordor-Hedgecock, P. Warner, R.H. Jones, K. Prout, *J. Organometallic Chem.*, **1985**, *285*, 213; (d) S.G. Davies, I.M. Dordor, J.C. Walker, P. Warner, *Tetrahedron Lett.*, **1984**, *25*, 2709; (e) L.S Liebeskind, M.E. Welker, V. Goedken, *J. Am. Chem. Soc.*, **1984**, *106*, 441; (f) L.S Liebeskind, M.E. Welker, R.W. Fengl, *J. Am. Chem. Soc.*, **1986**, *108*, 6328.

12 (a) S.G. Davies, I.M. Dordor-Hedgecock, P. Warner, *Tetrahedron Lett.*, **1985**, *26*, 2125; (b) L.S Liebeskind, M.E. Welker, *Tetrahedron Lett.*, **1984**, *25*, 4341; also ref. 11 (b), (c) and (f).

13 Oxford Asymmetry Limited, 57 Milton Park, Abingdon, Oxon, OX14 4RX, UK.

14 A. Horeau, H.-B. Kagan, J.-P. Vigneron, *Bull. Soc. Chim. Fr.*, **1968**, 3795.

15 (a) I Ojima, T. Kogura, M. Kumagai, *J. Org. Chem.*, **1977**, *42*, 1671; (b) T. Aratani, Y. Yoneyoshi, T. Noyase, *Tetrahedron Lett.*, **1977**, 2599; (c) R. Noyori, M. Suzuki, *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 847; (d) R.W. Hoffmann, H.-J. Zeiss, *Angew. Chem. Int. Ed. Engl.*, **1980**, *19*, 218.

16 C.H. Heathcock, C.T. White, J.J. Morrison, D. VanDerveer, *J. Org. Chem.*, **1981**, *46*, 1296; C.H. Heathcock, M.C. Pirrung, J. Lampe, C.T. Buse, S.D. Young, *J. Org. Chem.*, **1981**, *46*, 2290.

17 S. Masamune, W. Choy, J.S. Petersen, L.R. Sita, *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 1.

18 (a) R.P. Beckett, S.G. Davies, *J. Chem. Soc., Chem. Commun.*, **1988**, 160; (b) G.J. Bodwell, S.G. Davies, A.A. Mortlock, *Tetrahedron*, **1991**, *48*, 10077; (c) R.P. Beckett, S.G. Davies, A.A. Mortlock, *Tetrahedron Asymmetry*, **1992**, *3*, 123.

19 Y. Takemoto, T. Matsumoto, Y. Ito, S. Terashima, *Chem. Pharm. Bull.*, **1991**, *39*, 2425, see also refs 5a, 6a,b.

20 M.T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **1991**, *30*, 1531.

21 M.T. Reetz, M.W. Drewes, A. Schmitz, *Angew. Chem., Int. Ed. Engl.*, **1987**, *26*, 1141.

22 M. Cherest, H. Felkin, N. Prudent, *Tetrahedron Lett.*, **1968**, 2199; N.T. Anh, O. Eisenstein, *Nouv. J. Chem.*, **1977**, *1*, 61.

23 E.P. Lodge, C.H. Heathcock, *J. Am. Chem. Soc.*, **1987**, *109*, 3353.

24 M.T. Reetz, personal communication.

25 D. Parker, R.J. Taylor, *Tetrahedron*, **1987**, *43*, 2199.

26 A.J. Macuso, S.-L. Huang, D. Swern, *J. Org. Chem.*, **1978**, *43*, 2480.

27 D.B. Dess, J.C. Martin, *J. Org. Chem.*, **1983**, *48*, 4155.

28 C.R Schmid, J.D. Bryant, M. Dowlatzedah, J.L. Phillips, D.E. Prather, R.D. Schantz, N.L. Sear, C.S. Vianco, *J. Org. Chem.*, **1991**, *56*, 4056.

29 D.F. Shriver *The Manipulation of Air-Sensitive Compounds*; McGraw Hill, New York, 1969.