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Studies on the scope and applications of the catalysed asymmetric addition of organolithium reagents to imines

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Abstract: The sparteine induced asymmetric addition of organolithium reagents to α,β-unsaturated imines has been used to prepare non-racemic α-amino acids and their derivatives. The effect of various protecting groups for the nitrogen atom was investigated and *p*-methoxyphenyl derivatives were found to give the best enantiomeric excesses whilst trimethylsilyl protected imines were the most versatile for subsequent manipulation.
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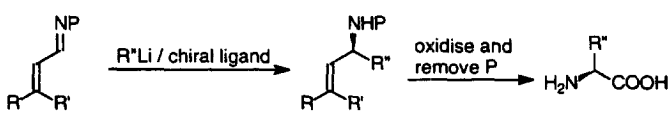
Introduction

A major goal in synthetic and bioorganic chemistry over the last decade has been the development of practical approaches to the synthesis of non-racemic α-amino acids. A large number of such syntheses have been developed, the majority of which are based around the use of chiral auxiliaries.[1] As part of an ongoing project concerned with the asymmetric addition of nucleophiles to imines,[2] we were attracted to a potential asymmetric synthesis of α-amino acids based on the addition of organolithium reagents to α,β-unsaturated imines as shown in Scheme 1. This synthetic approach has the advantages of being concise, employing starting materials that are readily available, and employing a chiral reagent rather than a chiral auxiliary, which both minimizes the number of synthetic steps required and offers the potential to use a chiral catalyst.



Scheme 1. Synthetic route to amino acids.

Compared to the corresponding additions to carbonyl compounds, the addition of organometallic reagents to imines presents a number of challenges due to the lower electrophilicity of imines, the possibility of *E,Z*-isomerism, and the need for a suitable protecting group for the nitrogen atom. For the present work, the possibility of competing 1,4-addition to the α,β-unsaturated imine also had to be considered. A number of chiral catalysts and/or chiral ligands for the asymmetric addition of organolithium reagents to imines have been developed, including; sparteine[3,4] **1**, bis-oxazolines[3] **2**, dialkyl-dihydrobenzoins[5] **3** and amino ethers[2,5,6] **4** and **5**. The catalytic, asymmetric addition of organometallic reagents to *N*-heteroatom substituted imines[7] and to nitrones[8] has also been reported. Of these various chiral ligands, the use of sparteine as reported by Denmark[3] appeared to produce the highest enantiomeric excesses. In this paper we report our investigations into the scope of the sparteine induced asymmetric addition of organolithium reagents to imines, and show how the adducts can be transformed into α-amino acids and their derivatives.

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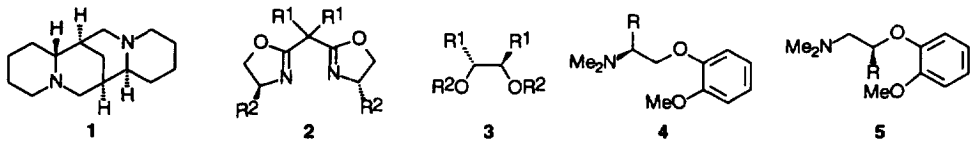
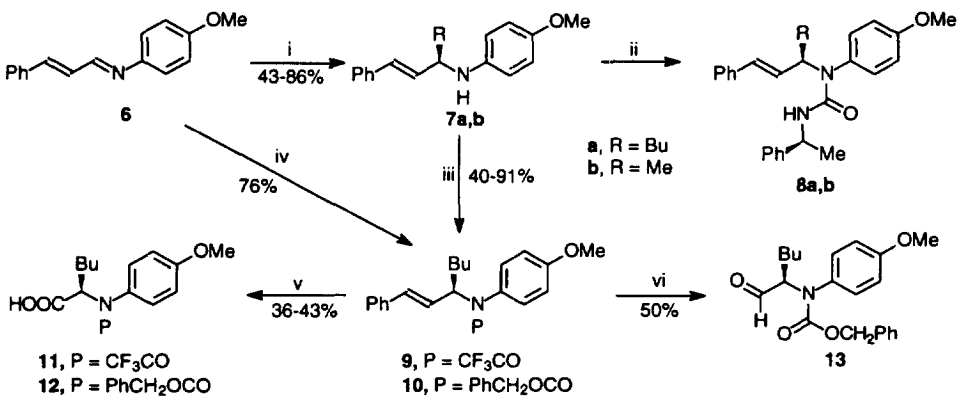


1 2 3 4 5

Results and discussion

Initially, imine **6** with a *p*-methoxyphenyl group protecting the nitrogen atom was chosen since literature precedent suggested that this would be compatible with good asymmetric induction and could be removed by mild oxidation.[3,5,6] The addition of both butyl and methyllithium to imine **6** was investigated in toluene and ether using varying amounts of (−)-sparteine as a chiral ligand as shown in Scheme 2. The reactions were carried out initially at −78°C, but in the case of methyllithium, reaction occurred only when the reaction mixture was subsequently allowed to warm to ambient temperature. Only one reaction was conducted with methyllithium since Denmark had previously investigated the reaction between imine **6** and methyllithium in the presence of sparteine.[3] The results of these optimization reactions are shown in Table 1. Racemic samples of amines **7a,b** were also prepared (by the same route but omitting the (−)-sparteine) to aid in enantiomeric excess determination and allow the subsequent chemistry to be developed. The enantiomeric excess of amines **7a,b** was determined by reaction with (*S*)-α-methylbenzylisocyanate to give ureas **8a,b** which could be analysed by HPLC (**7a**) or NMR (**7b**). Control reactions were carried out on racemic samples of amines **7a,b** to show that no kinetic resolution occurred during the derivatization. The absolute configuration of amine **8b** was known to be *R* by comparison with Denmark's results;[3] the absolute configuration of amine **8a** was not determined but is assumed to be *R* based on Denmark's work.[3] It is notable that the sparteine induced reaction gives best results in ether and with butyllithium, in contrast to our experiences[2] with amino ether derived ligands such as **4**.



Reagents: i) RLi / (-)-sparteine, ii) (*S*)-PhCH(Me)NCO, iii) $(CF_3CO)_2O$ / Et_3N or $PhCH_2OCOCl$ / BuLi, iv) BuLi / (-)-sparteine / $PhCH_2OCOCl$, v) $RuCl_3$ / $NaIO_4$, vi) O_3 / Me_2S

Scheme 2. Addition of organolithium reagents to imine **6** and subsequent transformations.

Having shown that enantiomeric excesses of greater than 75% could be obtained in the sparteine induced addition reaction, the conversion of the amines **7a,b** into the corresponding α-amino acids was investigated. All attempts to oxidize either the *p*-methoxyphenyl substituent or the alkene in the presence of an NH group proved unsuccessful, so it was necessary to introduce a second protecting group onto the amine. Both the *N*-trifluoroacetyl **9** and *N*-benzyloxycarbonyl **10** derivatives of amine **7a** could be prepared by reaction of the amine with trifluoroacetic anhydride and benzyl chloroformate respectively. Derivative **10** could also be prepared directly from imine **6** simply by quenching the butyllithium addition with benzyl chloroformate rather than with water as shown in Scheme 2.

Table 1. Addition of organolithium reagents to imine **6** in the presence of (−)-sparteine

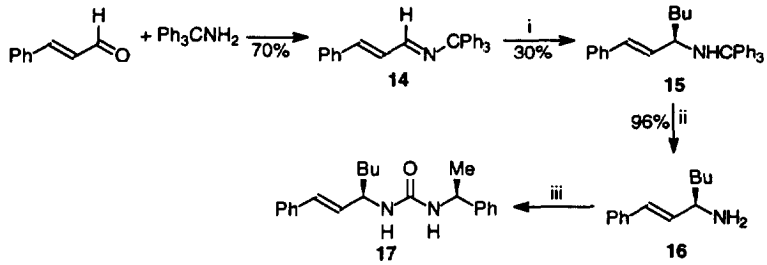
Imine	Solvent	RLi (eq.)	(-)-Sparteine (eq.)	Yield (%)	ee (%)[+]
6	toluene	BuLi (1.5)	0.2	43	48
6	toluene	BuLi (2.4)	1.0	66	70
6	ether	BuLi (2.4)	1.0	71	87
6	ether	BuLi (2.4)	1.1	86	88
6	ether	MeLi (1.0)	3.0	60	76 (*R*)
14	THF	BuLi (1.3)	1.1	35	13
14	ether	BuLi (1.0)	1.0	30	16
14	ether	BuLi (1.2)	1.1	24	25
14	ether	BuLi (1.6)	1.1	0	
14	ether	BuLi (2.0)	1.1	0	
14	toluene	BuLi (1.0)	1.0	30	28
18	hexane	BuLi (1.2)	1.0	0	
18	$^{i}Pr_2O$	BuLi (1.2)	1.0	0	
18	THF	BuLi (1.2)	1.1	40	0
18	toluene	BuLi (1.2)	1.0	40	32
18	ether	BuLi (1.2)	1.0	45	34
18	ether	MeLi (1.2)	1.2	39	16
18*	ether	BuLi (1.2)	1.1	48	44

[+] Except where otherwise specified, all reactions were carried out at -78°C. Full details are given in the experimental section. * Reaction carried out at -88°C.

The alkene in both compounds **9** and **10** could be oxidized to the corresponding carboxylic acids **11** and **12** by treatment with ruthenium(III) chloride and sodium periodate. The *N*-benzyloxycarbonyl derivative **10** could also be oxidized to aldehyde **13** by treatment with ozone followed by dimethyl sulfide (Scheme 2).

Unfortunately, all attempts to cleave the *p*-methoxyphenyl protecting group from compounds **9–12** proved unsuccessful. The standard conditions for removing this protecting group using ceric ammonium nitrate[9] were investigated, as were alternative procedures such as electrolysis,[10] ozonolysis[11] and oxidative cleavage using silver nitrate.[12] Hence alternative nitrogen protecting groups which could be removed under milder conditions were sought. A suitable protecting group needed to be easily formed and removed, contain no acidic hydrogens (thus excluding benzyl and benzhydryl) and not be electron withdrawing so as not to accelerate the uncatalysed addition. The two protecting groups which appeared to fit these requirements were triphenylmethyl and trimethylsilyl.

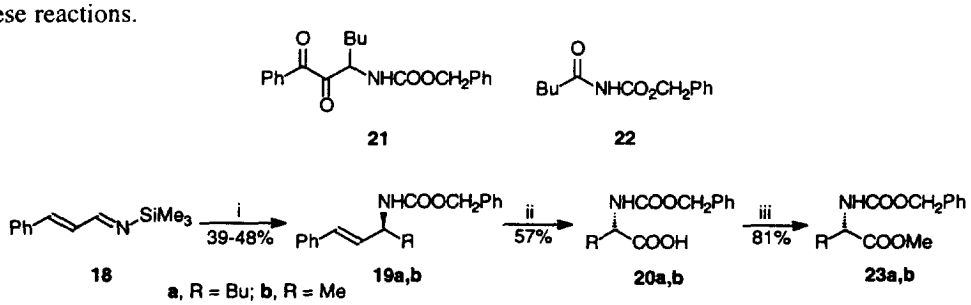
Surprisingly, there are only two literature reports of the synthesis of *N*-triphenylmethyl imines.[13] However, treatment of cinnamaldehyde with triphenylmethylamine in a Dean–Stark apparatus gave imine **14** in 70% yield as shown in Scheme 3. The sparteine induced addition of butyllithium to imine **14** was investigated in a range of solvents as shown in Table 1, with toluene being found to be a marginally superior solvent to ether in terms of chemical yield and enantiomeric excess. For all of these reactions, it was found necessary to allow the reaction mixture to warm to room temperature before quenching with water, otherwise only imine **14** was recovered. The enantiomeric excess of amine **15** was determined by removal of the *N*-triphenylmethyl protecting group using TFA to give the corresponding amine **16** followed by reaction with (*S*)-α-methylbenzylisocyanate to give urea **17**, which could be analysed by both ^{1}H NMR and HPLC. Oxidation of the alkene of compound **15** would provide a short synthesis of *N*-triphenylmethylamino acids. Unfortunately, all attempts to accomplish this transformation using ruthenium(III) chloride/sodium periodate or ozone were unsuccessful. It appeared that the combination of the large size and the acid lability of the triphenylmethyl group were causing problems. In view of these difficulties, no further efforts were made to optimize the chemical yield or enantiomeric excess of amine **15** and the use of a trimethylsilyl protecting group was investigated.



Reagents: i) BuLi / (-)-sparteine, ii) CF_3COOH, iii) (*S*)-PhCH(Me)-NCO

Scheme 3. Formation and reaction of imine **14**.

Imine **18** prepared by the literature procedure[14] was reacted with organolithium reagent in the presence of (−)-sparteine as shown in Scheme 4 and Table 1. In these reactions, it was necessary to add benzyl chloroformate after addition of the organolithium reagent, thus producing urethanes **19a,b** as the corresponding free amines could not be isolated from the reaction mixture. The enantiomeric excess of urethanes **19a,b** could be determined directly by chiral HPLC, and as the results in Table 1 show, ether was a marginally better solvent than toluene for this reaction with other solvents resulting in no addition or no asymmetric induction. Attempts were made to optimize the asymmetric induction observed during this reaction by varying the temperature, solvent, and sparteine/imine ratio (data not included in Table 1), however the best enantiomeric excess that could be obtained was 44% for amine **19a** and 16% for amine **19b**, values that are disappointingly lower than the values obtained for the addition of organolithium reagents to imine **6**. The absolute configuration of amines **19a,b** was determined by their subsequent manipulations, and in both cases the (*S*)-enantiomer of the amine is formed in excess. Interestingly, this is the opposite enantiomer to that obtained in excess during the addition of organolithium reagents to imine **6**[3] and illustrates that the nature of the nitrogen protecting group can have a profound effect on both the magnitude and direction of asymmetric induction obtained in these reactions.



Reagents: i) a, RLi / (-)-sparteine, b, $PhCH_2OCOCl$,c, H_3O^+, ii) $RuCl_3$ / HIO_4, iii) MeOH / HCl

Scheme 4. Addition of organolithium reagents to imine **18** and subsequent transformations.

Oxidation of alkenes **19a,b** to amino acid derivatives **20a,b** was achieved by treatment with ruthenium(III) chloride and periodic acid (Scheme 4). During the oxidation of compound **19a**, two by-products were identified, diketone **21** resulting from under oxidation of the alkene and urea **22** resulting from over oxidation, a process for which there is literature precedent.[15] The acids **20a,b** were converted to the corresponding methyl esters **23a,b** which could be analysed by chiral HPLC. Authentic samples of (*S*)- and (*R,S*)-**23a,b** were also prepared from (*S*)- or (*R,S*)-norleucine and (*S*)- or (*R,S*)-alanine by *N*-protection and esterification. Comparison of both the specific rotations and HPLC retention times of **23a,b** with the corresponding compounds prepared from the (*S*)-amino acids

clearly indicated that in both cases the (*S*)-enantiomer predominated, and the enantiomeric excess of compounds **23a,b** were the same as those of **19a,b**.

Conclusions

The (−)-sparteine induced addition of organolithium reagents to *N*-protected cinnamylimines followed by oxidative cleavage of the alkene group provides a short approach to the synthesis of non-racemic amino acids. Both the absolute configuration and the enantiomeric excess of the allylic amines produced in the first step are dependent upon the protecting group chosen for the nitrogen atom. Unfortunately, the best asymmetric induction is obtained using a *p*-methoxyphenyl protecting group which is the least versatile group for subsequent manipulation. Lower asymmetric induction is obtained with more versatile protecting groups such as triphenylmethyl and trimethylsilyl. Whether the large size of these protecting groups is associated with the low enantiomeric excesses is not yet clear.

Experimental

General experimental details have been reported elsewhere.[2] Chemical yields are unoptimized.

*Asymmetric alkylation of imine **6** using organolithium reagents in the presence (−)-sparteine*

The organolithium reagent (3.0 mmol) was added to a stirring solution of imine **6** (0.47 g, 2.0 mmol) and (−)-sparteine (0.5 to 4.0 mmol) in dry ether (70 ml) at −78°C under an inert atmosphere. The solution was stirred at this temperature for one hour, before quenching with water (20 ml). The ethereal solution was washed with 5% aqueous K_2CO_3 (50 ml), the aqueous layer extracted with EtOAc (50 ml) and the combined organic extracts washed with water (100 ml) and brine (100 ml). The organic layer was dried over K_2CO_3 before filtering and removing solvent *in vacuo*. The residue was purified by flash chromatography to yield the allylic amine as a yellow oil. The spectroscopic and analytical data for amines **7a,b** were consistent with those reported previously.[2]

*Formation of ureas using (S)-α-methylbenzylisocyanate and amines **7a,b** and **16***

(*S*)-α-Methylbenzylisocyanate (15 μl, 18 mg, 0.23 mmol) was added to a solution of amine **7a,b** and **16** (20 to 50 mg) in $CDCl_3$ (0.5 ml). The mixture was allowed to stand at room temperature for 24 hours or until the reaction had reached completion, before analysis by ^1H NMR spectroscopy and/or HPLC. The spectroscopic and analytical data for ureas **8a,b** were consistent with those reported previously.[2] Data for urea **17**: δ_H 0.9–1.0 (3H, m, CH_3), 0.9 (3H, 2×d, *J* 6.5, CH_3), 1.1–1.3 (6H, m, $(CH_2)_3$), 2.85 (2H, brs, 2×NH), 4.15–4.2 (1H, m, CH), 4.3 (1H, q, *J* 8.0, CH), 6.0 (1H, 2×dd, *J* 6.0 16.0, C*H*=CHPh), 6.2–6.4 (1H, 2×d, *J* 16.0, CH=C*H*Ph) and 7.1–7.3 (10H, m, ArCH); δ_C 14.0 CH_3, 22.5 CH_2, 23.5 CH_2, 27.6 CH_2, 27.9 CH_2, 35.3 CH_2, 35.5 CH_2, 50.4 CH, 52.4 CH, 128.0 CH, 125.8 CH, 127.3 CH, 128.4 CH, 128.8 CH, 130.0 CH, 131.3 CH, 144.0 ArC, 146.9 ArC, 156.3 CO and 157.1 CO; HPLC (isopropyl alcohol:hexane=1:1); 2.0 ml $min.^{-1}$: 2.52 min. (41%), 5.24 min. (24%), 25% ee.

*1-Phenyl-3-(N-benzyloxycarbonyl, p-methoxyphenylamino)-hept-1-ene **10** from imine **6***

^{n}BuLi (0.13 mol, 80 ml of a 1.6 M solution in hexanes) was added to a stirring solution of imine **6** (20 g, 0.084 mol) and (−)-sparteine (20 g, 0.086 mol) in dry ether (200 ml) at −78°C under an inert atmosphere. The solution was stirred at this temperature for one hour, before addition of benzyl chloroformate (21.5 g, 0.13 mol) after which the reaction was allowed to warm gradually to room temperature and stirred for five hours. The reaction mixture was washed with 2M HCl (2×200 ml), 5% aqueous K_2CO_3 solution (2×200 ml) and brine (200 ml) before drying over K_2CO_3. Filtration and removal of solvent *in vacuo* gave an orange oily residue which was purified by flash chromatography eluting with petrol:EtOAc (9:1) to yield (R_f 0.34) compound **10** as a yellow oil (27.5 g, 0.064 mol) in 76% yield. $[\alpha]_D^{25}$ −17.2 (*c* 1.0, $CHCl_3$); υ_{max} (film) 3020 m, 2937 s, 1694 s and 1612 cm^{-1} s; δ_H 0.9 (3H, t, *J* 7.0, CH_3), 1.2–1.4 (4H, m, $(CH_2)_2Me$), 1.4–1.6 (2H, m, $CHCH_2$), 3.8 (3H, s, OCH_3), 4.8–4.9 (1H, m, NCH), 5.2 (2H, s, $PhCH_2$), 6.1 (1H, dd, *J* 8.5, 16.0, C*H*=CHPh), 6.6 (1H, d, *J* 16.0,

CH=C*H*Ph), 6.9 (2H, d, *J* 9.0, ArCH *ortho* to OMe), 7.1 (2H, d, *J* 9.0, ArCH *meta* to OMe) and 7.2–7.4 (10H, m, C_6H_5); δ_C 14.1 CH_3, 22.6 CH_2, 28.7 CH_2, 32.9 CH_2, 55.4 OCH_3, 60.4 NCH, 66.9 CH_2Ph, 114.0 CH, 127.3 CH, 127.5 CH, 127.7 CH, 128.4 CH, 128.6 CH, 128.9 CH, 129.2 CH, 130.7 CH, 132.2 CH, 137.0 ArC, 155.9 ArC, 156.3 ArC and 158.7 NCO; m/z (CI, NH_3) 430 (MH^+, 100%) and 173 (80). [Found (CI, NH_3) MH^+, 430.2382. $C_{28}H_{32}NO_3$ requires *M*, 430.2384.]

*1-Phenyl-3-(*N*-trifluoroacetyl,* p*-methoxyphenylamino)-hept-1-ene* ***9***

To a stirred solution of amine **7a** (0.5 g, 1.7 mmol) in dichloromethane (30 ml) under an inert atmosphere, triethylamine (0.3 g, 0.30 mmol) was added, followed by trifluoroacetic anhydride (0.40 g, 1.86 mmol). The solution was stirred at room temperature for 18 hours before washing with 5% aqueous K_2CO_3 solution (30 ml), water (30 ml), and brine (30 ml) followed by drying over $MgSO_4$. Solvent was removed *in vacuo* to give a brown oily residue which was purified by flash chromatography using petrol:ether (19:1) as eluent. Trifluoroacetamide **9** was isolated (R_f 0.26) as a pale yellow oil (0.27 g, 0.7 mmol) in 40% yield. υ_{max} (film) 3031 m, 2942 s, 1689 s and 1610 cm^{-1} m; δ_H 0.95 (3H, t, *J* 6.5, CH_3), 1.3–1.4 (4H, m, $(CH_2)_2Me$), 1.6–1.7 (2H, m, $CHCH_2$), 3.8 (3H, s, OCH_3), 5.2 (1H, q, *J* 8.0, NCH), 5.9 (1H, dd, *J* 9.0, 16.0, C*H*=CHPh), 6.65 (1H, d, *J* 16.0, CH=C*H*Ph), 6.9–7.05 (4H, m, C_6H_4OMe) and 7.2–7.4 (5H, m, C_6H_5); δ_C 14.0 CH_3, 22.5 CH_2, 28.4 CH_2, 32.0 CH_2, 55.4 OCH_3, 60.3 NCH, 113.7 ArCH, 113.8 ArCH, 116.5 (q, J_{CF} 289, CF_3), 126.6 CH, 126.7 CH, 128.2 CH, 128.6 CH, 131.2 CH, 136.4 ArC, 159.9 ArC and 156.8 (q, J_{CF} 35, $COCF_3$); m/z (CI, NH_3) 409 ($M+NH_4^+$, 25%), 392 (MH^+, 10) and 173 (100). [Found (CI, NH_3) MH^+, 392.1837. $C_{22}H_{25}O_2NF_3$ requires *M*, 392.1839.]

*1-Phenyl-3-(*N*-benzyloxycarbonyl,* p*-methoxyphenylamino)-hept-1-ene* ***10*** *from amine* ***7a***

^{n}BuLi (3.8 ml, 5.11 mmol of a 1.34 M in hexanes solution) was added to a solution of amine **7a** (1.37 g, 4.65 mmol) in dry ether (100 ml) and stirred under an inert atmosphere at −78°C. The solution was stirred for 30 minutes before warming to room temperature for 10 minutes and cooling once again to −78°C after which benzyl chloroformate (0.87 g, 5.11 mmol) was added. Stirring was continued at room temperature for 18 hours before washing the reaction mixture with 2M HCl (75 ml), 5% aqueous K_2CO_3 solution (75 ml), water (75 ml) and brine (75 ml). The organic layer was dried over K_2CO_3 before removing solvent *in vacuo* to yield urethane **10** as an oil (1.9 g, 4.42 mmol) in 91% yield. Spectroscopic data were identical to those reported for the preparation of compound **10** from imine **6**.

N-*Trifluoroacetyl-*N*-(*p*-methoxyphenyl)-2-aminohexanoic acid* ***11***

To stirred solution of amide **9** (0.33 g, 0.84 mmol) in acetonitrile (6 ml), tetrachloromethane (6 ml) and water (9 ml), ruthenium(III) chloride trihydrate (60 mg, 0.23 mmol) and sodium periodate (1.90 g, 8.9 mmol) were added. The reaction mixture was stirred at room temperature for 18 hours before diluting with water (30 ml) and extracting into dichloromethane (3×30 ml). The organic extracts were combined and dried over $MgSO_4$ before filtering and removing solvent *in vacuo* to leave an oil which was purified by flash chromatography eluting with a solvent gradient from petrol:EtOAc (9:1), to 100% EtOAc to isolate the acid **11** as a colourless oil (100 mg, 0.30 mmol) in 36% yield (R_f 0.06; petrol:EtOAc=9:1). υ_{max} (film) 3500–3000 br, 3020 s, 2949 s, 1710 s and 1700 cm^{-1} s; δ_H 0.9 (3H, t, *J* 7.0, CH_3), 1.25–1.6 (4H, m, $(CH_2)_2Me$), 1.8–2.0 (2H, m, $CHCH_2$), 3.8 (3H, s, OCH_3), 4.7 (1H, dd, *J* 8.5, 6.0, NCH), 6.9 (2H, d, *J* 9.0, ArCH *ortho* to OMe), 7.3–7.4 (2H, m, ArCH *meta* to OMe) and 10.7 (1H, brs, CO_2H); δ_C 13.7 CH_3, 22.2 CH_2, 28.0 CH_2, 28.7 CH_2, 55.4 OCH_3, 63.1 NCH, 114.2 ArCH, 117.1 (q, J_{CF} 288, CF_3), 128.5 ArCH, 136.0 ArC, 157.8 (q, J_{CF} 36, $COCF_3$), 158.5 ArC and 176.0 CO_2H; m/z (CI, NH_3) 351 ($M+NH_4^+$, 100%) and 334 (MH^+, 10). [Found (CI, NH_3) $M+ NH_4^+$, 351.1532. $C_{15}H_{22}N_2O_4F_3$ requires *M*, 351.1533.]

N-*Benzyloxycarbonyl*-N-*(p-methoxyphenyl)-2-aminohexanoic acid* **12**

To a stirring solution of urethane **10** (0.163 g, 0.38 mmol) in acetonitrile (2 ml), tetrachloromethane (2 ml) and water (3 ml), ruthenium(III) chloride trihydrate (30 mg, 0.11 mmol) followed by sodium periodate (1.18 g, 5.54 mmol) were added and the resulting reaction mixture was stirred at room temperature for 18 hours. The solution was diluted with water (20 ml) and extracted into dichloromethane (3×20 ml). The organic extracts were combined and dried over $MgSO_4$ before filtering and removing solvent *in vacuo* to give a blackened oily residue which was purified by flash chromatography eluting with a solvent gradient from petrol:EtOAc (9:1) to 100% EtOAc to yield (R_f 0.09, petrol:EtOAc=1:1) acid **12** as a colourless oil (60 mg, 0.16 mmol) in 43% yield. υ_{max} (film) 3300 br, 3050 m, 2957 s and 1700 cm^{-1} s; δ_H 0.9 (3H, t, *J* 7.0, CH_3), 1.2–1.5 (4H, m, $(CH_2)_2Me$), 1.7–2.0 (2H, m, $CHCH_2$), 3.85 (3H, s, OCH_3), 4.6 (1H, dd, *J* 6.0, 9.0, NCH), 5.15 (2H, s, CH_2Ph), 6.9 (2H, d, *J* 9.0, ArCH *ortho* to OMe) and 7.2–7.5 (7H, m, ArCH); δ_C 13.8 CH_3, 22.2 CH_2, 28.7 CH_2, 37.3 CH_2, 55.4 OCH_3, 62.3 NCH, 72.2 CH_2Ph, 114.0 ArCH, 127.0 ArCH, 127.7 ArCH, 128.4 ArCH, 129.6 ArCH, 132.4 ArC, 138.6 ArC, 158.6 NCO, 159.2 ArC and 176.5 CO_2H; m/z (CI, NH_3) 389 ($M+NH_4^+$, 40%), 372 (MH^+, 100) and 328 (45). [Found (CI, NH_3) MH^+, 372.1811. $C_{21}H_{26}NO_5$ requires *M*, 372.1812.]

N-*Benzyloxycarbonyl*-N-*(p-methoxyphenyl)-2-aminohexanal* **13**

Urethane **10** (0.29 g, 0.67 mmol) was dissolved in methanol (100 ml), cooled to −78°C and treated with a stream of ozone. On completion of the reaction as indicated by the formation of a permanent steely blue colour, the solution was flushed with nitrogen and stirred with dimethyl sulphide (0.13 g, 2.1 mmol) at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* before diluting with water (70 ml) and extracting into ether (2×70 ml). The organic extracts were washed with 2M HCl (100 ml), 5% aqueous K_2CO_3 solution (100 ml), water (100 ml) and brine (100 ml), before drying over K_2CO_3. Solvent was removed *in vacuo* to give a yellow oily residue which was purified by flash chromatography eluting with petrol:EtOAc (4:1). Aldehyde **13** was isolated (R_f 0.44) as a pale yellow oil (0.12 g, 0.34 mmol) in 50% yield. υ_{max} (film) 3033 w, 2955 s, 1720 s and 1696 cm^{-1} s; δ_H 0.9 (3H, t, *J* 7.0, CH_3), 1.1–1.4 (4H, m, $(CH_2)_2Me$), 1.6–1.9 (2H, m, $CHCH_2$), 3.8 (3H, s, OCH_3), 4.3–4.4 (1H, m, NCH), 5.1 (2H, s, CH_2Ph), 6.8 (2H, d, *J* 9.0, ArCH *ortho* to OMe), 7.1 (2H, d, *J* 9.0, ArCH *meta* to OMe), 7.1–7.4 (5H, m, ArCH) and 9.8 (1H, s, CHO); δ_C 13.8 CH_3, 22.4 CH_2, 26.9 CH_2, 31.8 CH_2, 55.4 OCH_3, 68.7 NCH, 72.3 CH_2Ph, 114.3 ArCH, 127.2 ArCH, 128.3 ArCH, 128.4 ArCH, 129.4 ArCH, 132.1 ArC, 136.2 ArC, 156.0 ArC, 158.6 NCO and 199.6 CHO; m/z (CI, NH_3) 356 (MH^+, 100%). [Found (CI, NH_3) MH^+, 356.1862. $C_{21}H_{26}NO_4$ requires *M*, 356.1863.]

N-*Triphenylmethyl cinnamylimine* ***14***[13]

Triphenylmethylamine (3.71 g, 0.014 mol) and cinnamaldehyde (1.89 g, 0.014 mol) were dissolved in toluene (80 ml) and refluxed in a Dean–Stark apparatus for 3 hours. The reaction was then concentrated *in vacuo* to give a white solid residue which was recrystallized from ethanol (50 ml) to give a white crystalline solid (3.64 g, 0.01 mol) in 70% yield. Mp 156–157°C (lit. 155–156°C); υ_{max} (film) 3053 s, 2985 m and 1631 cm^{-1} s; δ_H 6.9 (1H, d, *J* 16.0, CH=C*H*Ph), 7.2–7.5 (19H, m, ArCH and C=CH), 7.5 (2H, d, *J* 8.0, ArCH) and 7.8 (1H, d, *J* 9.0, CH=N).

1-Phenyl-3-triphenylmethylamino-hept-1-ene ***15***

Imine **14** (0.39 g, 1.0 mmol) and (−)-sparteine (0.26 g, 1.1 mmol) were dissolved in dry ether (70 ml) and stirred under an inert atmosphere. The solution was cooled to −78°C and ^nBuLi (1.2 mmol, 0.75 ml of a 1.6 M in hexanes solution) was added, producing an orange colour. The reaction was maintained at −78°C for a further two hours before being allowed to warm gradually to room temperature and stirred for 48 hours. The reaction was quenched with 10% aqueous K_2CO_3 solution (50 ml) and washed successively with water (50 ml) and brine (50 ml) before drying over $MgSO_4$. The solution was then filtered and the solvent removed *in vacuo*. The residue was purified by flash

chromatography using hexane:EtOAc (20:1) as eluent to give amine **15** (R_f 0.28) as an oil (0.10 g, 0.24 mmol) in 24% yield. $[\alpha]_D^{25}$ −3.6 (*c* 1.0 in $CHCl_3$); υ_{max} (film) 4054 w, 3020 s, 2929 s and 1596 cm^{-1} s; δ_H 0.6 (3H, t, *J* 6.5, CH_3), 0.9–1.0 (6H, m, $(CH_2)_3$), 3.0 (1H, q, *J* 6.5, CH), 5.7 (1H, dd, *J* 16.0, 8.0, C*H*=CHPh), 5.9 (1H, d, *J* 16.0, CH=C*H*Ph), 7.0–7.2 (14H, m, ArCH) and 7.5 (6H, d, *J* 8.5, ArCH); δ_C 14.1 CH_3, 22.7 CH_2, 28.0 CH_2, 37.0 CH_2, 55.9 CH, 71.6 CPh_3, 126.2 ArCH, 126.4 ArCH, 126.8 ArCH, 127.5 ArCH, 127.8 ArCH, 128.4 ArCH, 128.7 ArCH, 129.6 ArCH, 133.7 ArC and 137.9 ArC; m/z (Ionspray) 431 (M^+, 3%), 243 (100) and 165 (25). [Found (Ionspray) M^+, 431.2598. $C_{32}H_{33}N$ requires *M*, 431.2613.]

1-Phenyl-3-amino-hept-1-ene ***16***

Amine **15** (0.1 g, 0.23 mmol) was dissolved in dichloromethane (5 ml) and water (5 ml). Trifluroacetic acid (0.13 g, 1.16 mmol) was added and the solution stirred for 45 minutes. The reaction mixture was diluted with 10% aqueous K_2CO_3 solution to give a pH of 8–10. This was then extracted with dichloromethane (2×20 ml) and the organic extracts were combined and dried over $MgSO_4$. The solution was then filtered and concentrated *in vacuo* to give amine **16** (0.1 g, 0.22 mmol) as a yellow oil in 96% yield which was used without further purification. δ_H 0.9 (3H, t, *J* 6.5, CH_3), 1.3–1.4 (4H, m, $(CH_2)_2$), 1.5–1.6 (2H, m, CH_2), 1.7–2.0 (2H, brs, NH_2), 3.4 (1H, q, *J* 6.5, CH), 6.1 (1H, dd, *J* 7.5, 16.0, C*H*=CHPh), 6.5 (1H, d, *J* 16.0, CH=C*H*Ph) and 7.2–7.4 (5H, m, ArCH); δ_C 14.0 CH_3, 22.7 CH_2, 28.4 CH_2, 37.6 CH_2, 54.2 CH, 127.9 CH, 126.2 CH, 127.2 CH, 128.5 CH, 128.9 CH and 146.8 ArC.

(S)-1-Phenyl-3-benzyloxycarbonylamino-hept-1-ene ***19a***

A solution of (−)-sparteine (0.5 g, 2.1 mmol) and imine **18**[14] (0.39 g, 1.9 mmol) in dry ether (70 ml) was stirred under an inert atmosphere at −78°C. ^{n}BuLi (2.16 mmol, 1.35 ml of a 1.6 M in hexanes solution) was added producing a deep green colour. The solution was stirred at −78°C for a further 1 hour after which benzyl chloroformate (0.36 g, 2.1 mmol) was added producing a red colour. The reaction mixture was allowed to warm gradually to room temperature and was stirred for 15 hours. The reaction was diluted with EtOAc (50 ml) and washed with 10% aqueous K_2CO_3 solution (100 ml). The aqueous washings were back extracted with EtOAc (50 ml) and the combined organic extracts were washed with 2M HCl (100 ml), water (100 ml) and brine (100 ml) before being dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give an oil which was purified by flash chromatography eluting with hexane:EtOAc (9:1) to give a creamy white solid which was recrystallized from hexane to give compound **19a** (0.3 g, 0.93 mmol) as a white crystalline solid in 48% yield. Mp 61–65°C (hexane); $[\alpha]_D^{24}$ −15.4 (*c* 1.065 in $CHCl_3$); (Found: C, 78.0; H, 7.65; N, 4.2%. $C_{21}H_{25}NO_2$ requires: C, 78.0; H, 7.8; N, 4.3%); υ_{max} (KBr) 3309 s, 3030 m, 2929 s, 1682 s and 1540 cm^{-1} s; δ_H 0.8 (3H, t, *J* 6.5, CH_3), 1.2–1.3 (4H, m, $(CH_2)_2$), 1.5–1.6 (2H, m, CH_2), 4.2 (1H, quintet, *J* 7.0, C*H*), 4.6 (1H, brs, NH), 5.2 (2H, s, OCH_2), 6.0 (1H, dd, *J* 6.5, 16.0, C*H*=CHPh), 6.4 (1H, d, *J* 16.0, CH=C*H*Ph) and 7.1–7.3 (10H, m, ArCH); δ_C 14.0 CH_3, 22.4 CH_2, 27.9 CH_2, 35.2 CH_2, 53.2 CH, 66.6 CH_2, 128.5 CH, 126.3 CH, 127.4 CH, 128.0 CH, 128.3 CH, 128.8 CH, 130.1 CH, 130.2 CH, 136.5 ArC, 136.6 ArC and 155.7 CO; m/z (Ionspray) 323 (M^+ 10%), 232 (40) and 91 (100). [Found (Ionspray) M^+, 323.1884. $C_{21}H_{25}NO_2$ requires *M*, 323.1885.] Chiral HPLC (hexane:isopropyl alcohol=1:1); 2.0 ml min^{-1}: 2.94 min. (72%), 5.60 min. (28%), 44% ee.

(S)-1-Phenyl-3-benzyloxycarbonylamino-but-1-ene ***19b***

The procedure was as described for compound **19a** using (−)-sparteine (1.23 g, 3.8 mmol), imine **18**[14] (0.65 g, 3.2 mmol) and MeLi (3.8 mmol, 2.7 ml of a 1.4 M in ether solution). The product was purified by flash chromatography eluting with hexane:EtOAc (5:1) (R_f 0.21) followed by recrystallization from hexane to give compound **19b** (0.42 g, 1.5 mmol) as a white crystalline solid in 39% yield. Mp 61–64°C (hexane); $[\alpha]_D^{26}$ −2.10 (*c* 2.74 in $CHCl_3$); υ_{max} (film) 3439 w, 3066 m, 2980 m, 1718 s and 1609 cm^{-1} m; δ_H 1.3 (3H, d, *J* 7.0, CH_3), 4.5–4.6 (1H, m, NCH), 4.8–4.9 (1H, m, NH), 5.1 (2H, s, CH_2Ph), 6.1 (1H, dd, *J* 6.0, 16.0, C*H*=CHPh), 6.5 (1H, d, *J* 16.0, =CHPh) and

7.3–7.4 (10H, m, ArCH); δ_C 21.1 CH_3, 59.0 CH, 66.7 CH_2, 126.4 CH, 127.6 CH, 128.1 CH, 128.2 CH, 128.5 CH, 128.8 CH, 130.0 CH, 131.1 CH, 134.3 ArC, 136.6 ArC and 165.2 NCO; m/z (CI, NH_3) 282 (MH^+, 5%) and 131 (100). [Found (CI, NH_3) MH^+, 282.1494. $C_{18}H_{20}NO_2$ requires *M*, 282.1494.] Chiral HPLC (hexane:isopropyl alcohol=1:1); 2.0 ml min^{-1}: 3.36 min (58%), 8.38 min (42%), 16% ee.

(S)-N-Benzyloxycarbonyl norleucine ***20a***[16]

Periodic acid (1.06 g, 4.5 mmol) was added in four equal amounts over a period of one hour to a stirring solution of compound **19a** (0.32 g, 1.0 mmol) in acetonitrile (4 ml), tetrachloromethane (4 ml) and water (6 ml) at 35–40°C. Ruthenium(III) chloride trihydrate (6 mg, 0.03 mmol) was subsequently added and the reaction stirred at this temperature for 18 hours. The reaction was diluted with water (10 ml) and extracted into EtOAc (3×20 ml). The combined organic extracts were dried over $MgSO_4$ before filtration and concentration *in vacuo* to give a dark red residue. The residue was redissolved in EtOAc (20 ml) and washed with saturated aqueous $NaHCO_3$ solution (2×20 ml). The organic layer was dried over $MgSO_4$ before filtration and concentration *in vacuo* to give an oily residue (0.07 g). The basic extracts were acidified to pH 2 using 2M HCl and extracted with EtOAc (2×50 ml). The EtOAc extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a mixture of acid **20a** and benzoic acid. The residue containing the neutral or basic products was purified by flash chromatography eluting with hexane:EtOAc (6:1) to yield two products, diketone **21** (R_f 0.19) (0.03 g, 0.085 mmol, 8.5% yield) and imide **22** (R_f 0.11) (0.04 g, 0.17 mmol, 17% yield). The acidic products were separated by flash chromatography eluting with EtOAc to yield (R_f 0.16) acid **20a** (0.15 g, 0.57 mmol) as a colourless oil in 57% yield.

Diketone **21**: υ_{max} (film) 3154 w, 3030 w, 2961 m, 1793 m, 1750 m and 1711 cm^{-1} s; δ_H 0.8 (3H, t, *J* 7.0, CH_3), 1.3–1.4 (4H, m, $(CH_2)_2$), 1.6–1.7 (1H, m, CH_2), 1.9–2.0 (1H, m, CH_2), 4.9 (1H, m, CH), 5.0 (2H, s, CH_2Ph), 5.2 (1H, d, *J* 8.0, NH) and 7.2–7.6 (10H, m, ArCH); δ_C 13.8 CH_3, 22.2 CH_2, 26.2 CH_2, 35.8 CH_2, 67.8 CH_2Ph, 70.0 CH, 127.5 ArCH, 128.0 ArCH, 128.5 ArCH, 129.3 ArCH, 130.1 ArCH, 133.6 ArCH, 135.0 ArC, 151.6 NCO, 170.8 CO and 174.8 CO; m/z (Ionspray) 353 (M^+, 10%), 220 (23), 105 (31) and 91 (100). [Found (Ionspray) M^+, 353.1610. $C_{21}H_{23}NO_4$ requires *M*, 353.1627.]

Imide **22**: υ_{max} (film) 3397 w, 2962 m, 1792 m, 1759 m and 1711 cm^{-1} s; δ_H 0.8 (3H, t, *J* 7.5, CH_3), 1.3 (2H, sextet, *J* 7.5, CH_2), 1.5 (2H, m, CH_2), 2.7 (2H, t, *J* 7.5, CH_2), 5.1 (2H, s, CH_2Ph) 5.2 (1H, br, NH) and 7.3–7.4 (5H, m, ArCH); δ_C 13.8 CH_3, 22.2 CH_2, 26.2 CH_2, 35.8 CH_2, 67.8 CH_2Ph, 128.2 ArCH, 128.4 ArCH, 128.7 ArCH, 135.0 ArC, 151.6 NCON and 174.6 NCO; m/z (Ionspray) 235 (M^+, 12%), 107 (75) and 91 (100). [Found (Ionspray) M^+, 235.1206. $C_{13}H_{17}NO_3$ requires *M*, 235.1208.]

Acid **20a**: $[\alpha]_D^{26}$ +1.35 (*c* 3.0 in $CHCl_3$) [a sample prepared from (*S*)-norleucine gave $[\alpha]_D^{24}$ +3.2 (*c* 2.0 in $CHCl_3$)]; υ_{max} 3500–3000 br, 3432 m and 1715 cm^{-1} s; δ_H 0.8–0.9 (3H, m, CH_3), 1.3–1.4 (4H, m, $(CH_2)_2$), 1.6–1.7 (1H, m, CH_2), 1.8–1.9 (1H, m, CH_2), 4.35 (1H, q, *J* 7.0, CH), 5.0 (2H, s, CH_2Ph), 5.2 (1H, d, *J* 8.5, NH), 7.2–7.3 (5H, m, ArCH) and 9.3 (1H, br, COOH); δ_C 13.8 CH_3, 22.2 CH_2, 27.2 CH_2, 32.0 CH_2, 53.7 CH, 67.1 CH_2Ph, 128.1 ArCH, 128.2 ArCH, 128.5 ArCH, 136.1 ArC, 156.3 NCO_2, 177.1 COOH; m/z (CI, NH_3) 283 ($M+NH_4^+$, 15%), 108 (40) and 86 (100).

(S)-N-Benzyloxycarbonyl norleucine methyl ester ***23a***[17]

Acid **20a** of 38% ee (0.1 g, 3.8 mmol) was stirred in a methanolic solution of anhydrous HCl for 17 hours after which time the solvent was evaporated *in vacuo* to yield an oily residue. This was purified by flash chromatography eluting with hexane:EtOAc (8:1) to yield compound **23a** (0.096 g, 0.34 mmol) as a viscous oil in 81% yield. $[\alpha]_D^{26}$ +3.5 (*c* 0.7 in $CHCl_3$) [A sample prepared from (*S*)-norleucine gave $[\alpha]_D^{24}$ +9.2 (*c* 1.0 in $CHCl_3$)]; υ_{max} (film) 3320 s, 2959 and 1724 cm^{-1} s; δ_H 0.8 (3H, t, *J* 7.0, CH_3), 1.2–1.3 (4H, m, $(CH_2)_2$), 1.6–1.7 (1H, m, CH_2), 1.7–1.8 (1H, m, CH_2), 3.65 (3H, s, OCH_3), 4.3 (1H, q, *J* 7.0, CH), 5.1 (2H, s, CH_2Ph), 5.75 (1H, d, *J* 8.5, NH) and 7.2–7.3 (5H, m, ArCH); m/z (CI, NH_3) 297 ($M+NH_4^+$, 42%), 280 (MH^+, 50) and 189 (100). Chiral HPLC (hexane:isopropyl alcohol=9:1); 2.0 ml min^{-1}: 5.56 min (69%), 6.56 min (31%), 38% ee. A sample

prepared from (*S*)-norleucine eluted as a single peak with a retention time of 5.54 min whilst a sample prepared from (*R,S*)-norleucine gave peaks of equal intensity at retention times of 5.60 and 6.61 min when analysed under identical conditions.

(S)-N-Benzyloxycarbonyl alanine methyl ester ***23b***[18]

Periodic acid (0.21 g, 0.92 mmol) was added in four equal amounts over a period of one hour to a solution of amine **19b** (0.027 g, 0.1 mmol) in acetonitrile (1 ml), tetrachloromethane (1 ml) and water (1.5 ml) at 35–40°C. Ruthenium(III) chloride hydrate (3 mg, 0.015 mmol) was added and the reaction stirred at this temperature overnight. The reaction was diluted with water (10 ml) and extracted into CH_2Cl_2 (3×20 ml). The combined organic extracts were dried over $MgSO_4$ before filtration and concentration *in vacuo* to give a dark red residue. The residue (0.032 g) was treated with methanolic HCl solution for 17 hours before removing solvent *in vacuo* to give compound **23b** (0.02 g) as a colourless oil in 84% yield. $[\alpha]_D^{22}$ −1.4 (*c* 2.57 in $CHCl_3$) [A sample prepared from (*S*)-alanine gave $[\alpha]_D^{22}$ −5.8 (*c* 1.2 in $CHCl_3$)]; υ_{max} (film) 3341 s, 3033 w, 2953 s and 1720 cm^{-1} s; δ_H 1.4 (3H, d, *J* 7.0, CH_3), 3.7 (3H, s, OCH_3), 4.4 (1H, quintet, *J* 7.5, CH), 5.1 (2H, s, CH_2Ph), 5.4 (1H, brs, NH) and 7.3–7.4 (5H, m, ArCH); δ_C 18.5 CH_3, 49.6 CH, 52.4 OCH_3, 66.9 CH_2Ph, 128.0 ArCH, 128.1 ArCH, 128.5 ArCH, 136.3 ArC, 155.6 NCO and 173.5 CO_2; Chiral HPLC (hexane:isopropyl alcohol=7:3): 2.0 ml min^{-1}: 3.98 min (56%), 4.52 min (39%), 17.8% ee. A sample prepared from (*S*)-alanine eluted as a single peak with a retention time of 3.64 min whilst a sample prepared from (*R,S*)-alanine gave peaks of equal intensity at retention times of 3.64 and 4.48 min when analysed under identical conditions.

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