N-Acyl 'Quat' pyrrolidinone auxiliary as a chiral amide equivalent *via* direct aminolysis

Stephen G. Davies* and Darren J. Dixon

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY

Received (in Cambridge, UK) 31st May 2002, Accepted 3rd July 2002
First published as an Advance Article on the web 18th July 2002

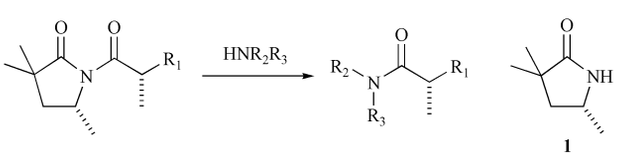
A novel route to chiral amides through the efficient, non-racemising, cleavage of *N*-acyl side chains from a 'Quat' chiral auxiliary using *N*-centred nucleophiles is described. The synthetic utility of the procedure is then highlighted by the preparation of a range of succinamide and succinimide derivatives and through the synthesis of the natural product (*S*)-(+)-amphetamine *via* a stereospecific Hofman type degradation using a hypervalent iodine reagent.

Introduction

The majority of naturally occurring substances containing the amide bond carry a stereogenic centre adjacent to the amidic carbonyl. This, combined with the vast number of naturally occurring peptides and pseudopeptides eliciting interesting biological and pharmacological properties, highlights the need for more efficient asymmetric routes to such important structural moieties.

The chiral auxiliary has played a regular role in the synthesis of the key, homochiral fragments contained within many of these pseudopeptides and related compounds.[1] Generally, the chiral auxiliaries are cleaved hydrolytically to afford the carboxylic acid which is then activated and coupled to an amine or a suitably protected α-amino acid through standard procedures.

Recently, we reported a conceptually more simple route to such chiral amides and pseudopeptides *via* direct aminolysis of the 'Quat' pyrrolidinone auxiliary **1**[2] from attached chiral side chains,[3] Scheme 1.



1

Scheme 1

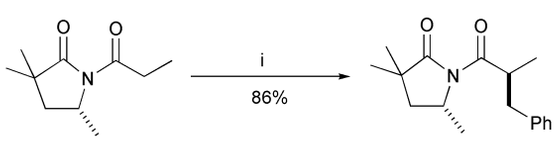
We found that efficient, non-racemising cleavage of *N*-α-methylhydrocinnamoyl side chains from the 'Quat' pyrrolidine auxiliary with a range of *N*-centred nucleophiles was possible leading to the production of chiral amides and we wish to report herein the full experimental details of these reactions. In addition, we report an extension of the methodology to encapsulate the efficient asymmetric synthesis of succinamide derivatives and highlight the utility of such a process in the synthesis of the natural product (*S*)-(+)-amphetamine.

The pyrrolidinone auxiliary **1** has been shown to induce high diastereoselectivities in both enolate alkylation[4] and aldol reactions[5] of attached acyl side chains. This combined with the exceptional propensity for exocyclic- over endocyclic-cleavage with *O*-centred nucleophiles, through steric blocking of the ring carbonyl by the geminal dimethyl groups, made pyrrolidinone **1** ideally suited as a precursor to chiral amides through direct aminolysis pathways.

Interestingly, there have been only a few reports of the direct cleavage from other chiral auxiliaries of chiral *N*-acyl side chains with either ammonia or amines.[6] The majority of these involve chiral auxiliaries with a high sulfur content which have been synthesised and utilised for, amongst other qualities, their lability towards nucleophilic reagents.[7–9] However, chiral auxiliaries of this type are severely restricted in terms of the number of types of asymmetric transformations which attached *N*-acyl side chains can undergo, with tin(II)-mediated aldol reactions being the most common.

Results and discussion

In our initial studies into the aminolysis of *N*-acyl 'Quat' derivatives, one of the simplest chiral side chains, namely *N*-α-methylhydrocinnamoyl, was chosen as the acyl donor equivalent. Thus starting material **3** was readily prepared in 86% yield and with >96% de by the benzylation of *N*-propionoyl 'Quat' **2** using LDA and benzyl bromide following standard procedures, Scheme 2.



2 **3**

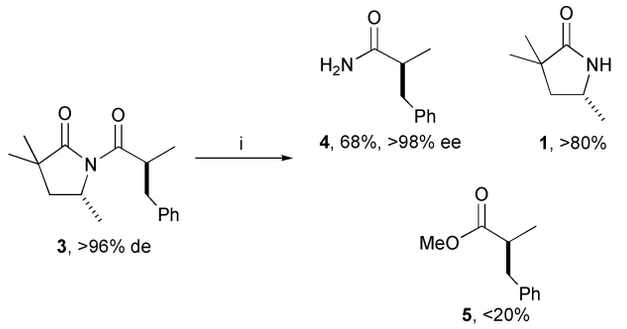
Scheme 2 *Reagents and conditions:* i) LDA, THF, −78 °C, 1 hour then benzyl bromide (3 eq.), −78 °C to RT.

In the first case, **3** was treated with a saturated solution of ammonia in methanol at 0 °C for 2 hours. Removal of volatiles *in vacuo* and trituration of the resulting material with pentane afforded the desired primary amide **4** as a colourless solid in 68% yield. Inspection of the ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the triturand indicated the presence of the pyrrolidinone **1** as the major component and methyl ester **5** as the minor, Scheme 3.

The specific rotation, $[\alpha]_D^{24}$ +55.4 (*c* 0.675, EtOH); [lit.,[10] $[\alpha]_D^{21}$ +53.1 (*c* 2.5, EtOH)] and melting point, mp 114–115 °C [lit.,[10] 113–114 °C] of **4** were in good agreement with the reported data. A ^{1}H NMR (300 MHz, $CDCl_3$) chiral shift experiment[11] with Eu(hfc)$_3$ showed the ee of amide **4** to be >98%. Clearly, this higher than expected enantiomeric excess had arisen through the trituration process and gave no indication of the amount, if any, of racemisation occurring during the cleavage process.

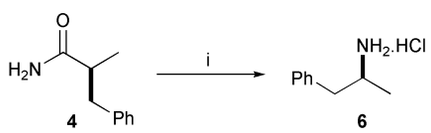
This preliminary result was particularly significant, for not only did it show that direct aminolysis of chiral side chains

DOI: 10.1039/b205326h



Scheme 3 *Reagents and conditions:* i) MeOH, NH_3 (g), 0 °C, 2 hours.

from the 'Quat' chiral auxiliary was possible, but also that the chiral amide product was a direct precursor to (*S*)-(+)-amphetamine through the Hofmann degradation.[12] Thus to highlight the utility of this primary amide product and the direct aminolysis procedure the Hofmann degradation was performed.[13] Treatment of **4** with 1.5 equivalents of [bis-(trifluoroacetoxy)iodo]benzene[14] in acetonitrile–water (1 : 1) at room temperature for 5 hours followed by aqueous work up gave (*S*)-(+)-amphetamine HCl salt **6** (Scheme 4) in 91%

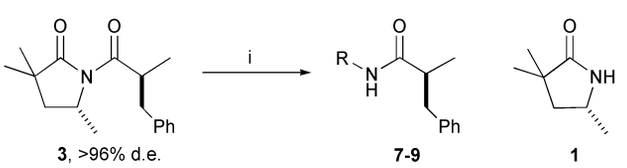


Scheme 4 *Reagents and conditions:* i) $PhI(OOCCF_3)_2$, CH_3CN–H_2O (1 : 1), RT, 5 hours.

yield. The melting point mp 156–157 °C [lit.[15] mp 156 °C] and the specific rotation $[\alpha]_D^{21}$ +25.9 (*c* 1.00, H_2O) [lit.,[15] $[\alpha]_D^{15}$ +24.8 (*c* 9, H_2O), lit.,[16] $[\alpha]_D^{20}$ +27.5 (*c* 1.00, H_2O)] were in good agreement with the reported data. The ee of **4** was determined as >98% by derivatisation as the Mosher's amide.

When unhindered primary amines were used in the aminolysis of **3** by far the best reaction conditions were simply to dissolve the starting material in neat amine (6 eq.) and allow the reaction mixture to stir at room temperature until all the starting material had been consumed (Scheme 5, Table 1).

For both allylamine and benzylamine the time for complete conversion was around 36 hours. When *tert*-butyl glycinate was

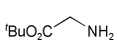
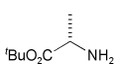


Scheme 5 *Reagents and conditions:* i) RNH_2, neat, RT.

used as the *N*-centred nucleophile the time increased considerably to 120 hours, presumably as a result of the lower nucleophilicity of the nitrogen in the aminoester. In all three cases however, the yields of the product amides, **7**–**9**, and the recovered auxiliary **1** were excellent. With α-substituted primary amines such as (*R*)- and (*S*)-α-methylbenzylamine or *tert*-butyl alaninate, no cleavage reaction was observed, even on prolonged standing at room temperature and with the amine as solvent (Entries 4–6). This was presumably the result of strongly destabilising steric interactions in the transition state leading to cleavage products. All attempts to rectify this situation by using co-solvents or elevated temperatures failed.

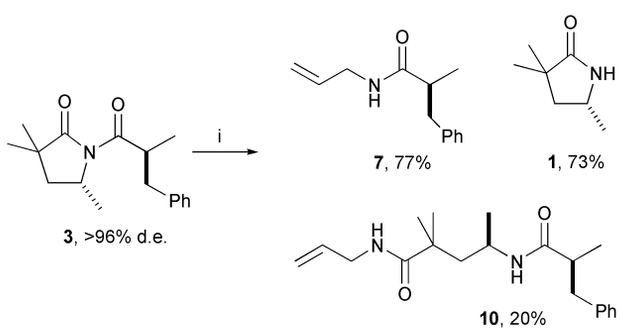
A ^1H NMR (300 MHz, $CDCl_3$) chiral shift experiment with $Eu(hfc)_3$ showed the ee of (*S*)-7 to be >96%. This value was in accordance with the diastereomeric excess of *N*-α-methylhydrocinnamoylpyrrolidinone and confirmed that cleavage with allylamine was occurring without racemisation. Although the enantiomeric excesses of **8** and **9** could not be measured

Table 1 Direct aminolysis reactions of **3** with primary amines

Entry	RNH_2	Eq.	Time/h	Amide (%)	**1** (%)
1		6	36	**7** (98)	97
2		6	36	**8** (96)	92
3		6	120	**9** (99)	98
4		xs	240	0	0
5		xs	240	0	0
6		6	240	0	0

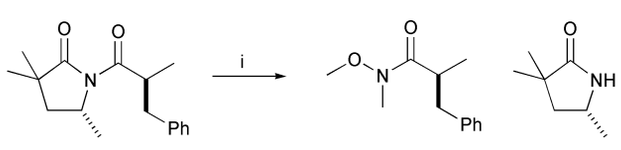
directly, they were assumed to be >96% by analogy with the measured ee of (*S*)-**7**.

Shorter aminolysis reaction times were realised when the requisite dimethylaluminium amides were used as the *N*-centred nucleophiles in the cleavage reactions instead of the parent amines. For example, treatment of **3** with an excess of dimethylaluminium allylamide in refluxing dichloromethane for 4 hours was sufficient for complete conversion. Aqueous work up and purification afforded allylamide **7** and pyrrolidine auxiliary **1** in 77% and 73% yields respectively. A ^1H NMR (300 MHz, $CDCl_3$) chiral shift experiment with $Eu(hfc)_3$ showed the ee of allylamide **7** to be >96%, confirming that cleavage was indeed occurring without racemisation. Interestingly, some of the endocyclic cleavage product **10** (20%) was also isolated from the reaction mixture, Scheme 6.



Scheme 6 *Reagents and conditions:* i) dimethylaluminium allylamide (3.0 eq.), Δ, 4 hours.

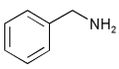
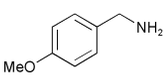
Efficient aminolysis to the synthetically versatile Weinreb amide **11** was also possible using the aluminium amide approach. Treatment of a dichloromethane solution of **3** with chloromethylaluminium *N*,*O*-dimethylhydroxyamide, at room temperature and then reflux, afforded the Weinreb amide **11** and the pyrrolidinone auxiliary **1** both in good yield, Scheme 7.



Scheme 7 *Reagents and conditions:* i) *N*,*O*-dimethylhydroxyamine·HCl, Me_3Al, CH_2Cl_2, RT, 22 hours then Δ, 3 hours.

No evidence of endocyclic attack was observed in the above reaction. This is in direct contrast to the analogous cleavages of *N*-acyloxazolidin-2-ones with side chains *not* bearing heteroatom substituents in either the α- or β-positions. In these cases the reactions may be dominated by endocyclic attack.[17,18]

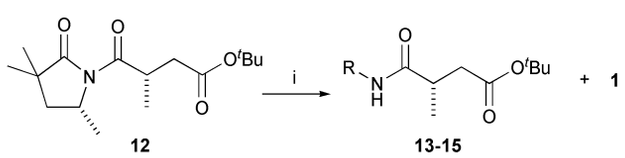
Table 2 Formation of amides **13**–**15** from **12**

Entry	RNH_2	Amide (%)	**1** (%)
1		**13** (95)	97
2		**14** (96)	92
3		**15** (89)	94

Accordingly, this result highlights the utility of pyrrolidinone **1** as an important precursor to chiral aldehydes and ketones.

It was apparent from the preliminary investigations described above that the direct cleavage of the *N*-acylpyrrolidinones with *N*-centred nucleophiles (either as the free amines or as the requisite aluminium amides) could be applied to the synthesis of a large range of important chiral compounds. Of particular interest are the homochiral alkylsuccinate family and in particular homochiral alkyl succinamides and alkyl succinimides, since these motifs can be found in a range of biologically and pharmacologically important compounds ranging from the hydroxamate matrix metalloproteinase (MMP) inhibitors such as Kelatorphan[19] to natural products such as the toxic alkaloid methyllycaconitine[20] and the potent pseudopeptide antibiotic andrimid.[21]

Thus *N*-methylsuccinylpyrrolidinone, readily available in two steps from the 'Quat' chiral auxiliary on multigram scales and in ≥95% de, was treated with an excess (6 eq.) of allylamine, benzylamine and *p*-methoxybenzylamine following the procedure described above. After 36 hours, the respective reaction mixtures were worked-up and the crude reaction products purified by chromatography on silica gel to afford, in each case, both the respective succinamide *tert*-butyl ester [**13**, **14** and **15**] and pyrrolidinone **1** in excellent yields, Scheme 8, Table 2.

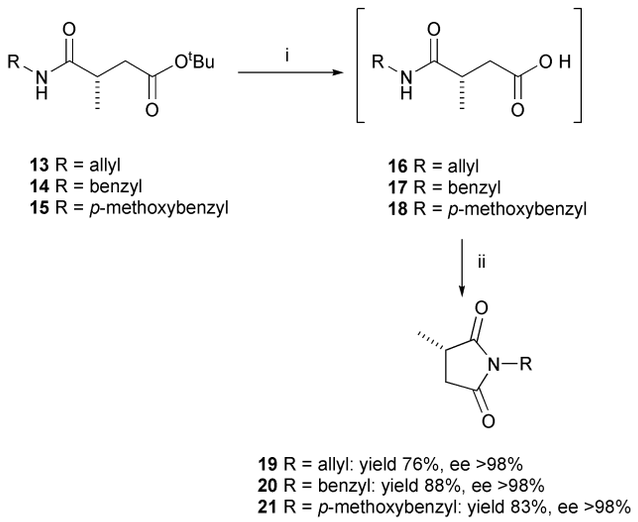


Scheme 8 *Reagents and conditions:* i) amine, neat, RT, 36 hours.

With the succinamide *tert*-butyl esters **13**, **14** and **15** in hand, a final cyclisation step was then required to complete the asymmetric synthesis of the differentially *N*-protected (*S*)-methylsuccinimides.

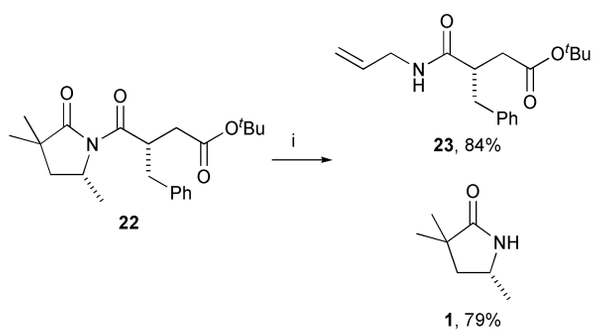
Although a one-step base-mediated cyclisation was possible, on related substrates this had caused considerable racemisation.[22] Accordingly, a two step deprotection–activation protocol was adopted. First, succinamide *tert*-butyl esters **13**, **14** and **15** were treated with trifluoroacetic acid at room temperature for 1 hour. Removal of the volatiles *in vacuo*, afforded the intermediate half acids **16**, **17** and **18** respectively, which were characterised solely by mass spectrometry [**16**; *m*/*z* (APCI$^-$) 170 (M − H$^+$), **17**; *m*/*z* (APCI$^-$) 220 (M − H$^+$) and **18**; *m*/*z* (APCI$^-$) 250 (M − H$^+$)]. These half acids were then dissolved in dichloromethane, treated with 1,1′-carbonyldiimidazole (CDI, 1.5 eq.) and stirred at room temperature overnight. Protic work-up and purification by chromatography on silica gel, afforded the respective succinimides, **19**, **20** and **21**, each in good yield, Scheme 9.

Following the procedure of Puertas *et al.*, a ^{1}H NMR (300 MHz, $CDCl_3$) chiral shift experiment with Eu(hfc)$_3$ showed the ee of **19** to be >98%.[22] Although the enantiomeric excesses of **20** and **21** could not be measured directly, they were assumed to be >98% by analogy with the measured ee of **19**.



Scheme 9 *Reagents and conditions:* i) TFA, RT; ii) CDI (1.5 eq.), CH_2Cl_2, RT, overnight.

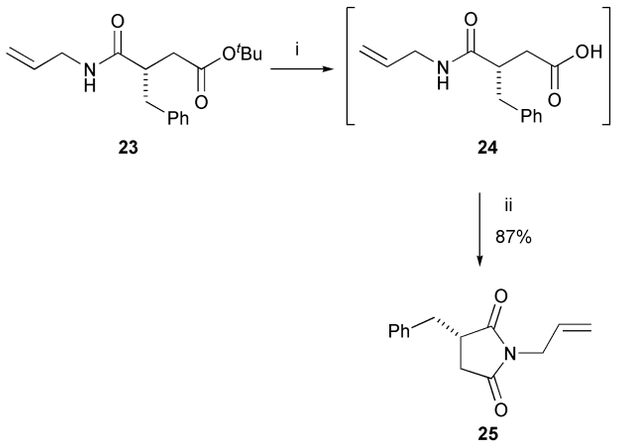
In a similar fashion to the above, *N*-benzylsuccinylpyrrolidinone **22**, readily available in two steps from the 'Quat' chiral auxiliary on a multigram scale and in ≥98% de, was treated with a large excess of allylamine in the absence of a solvent at room temperature for 5 days. Removal of the excess amine and purification by chromatography on silica gel afforded the succinate derivative **23** and the pyrrolidinone auxiliary **1** each in good yield, Scheme 10.



Scheme 10 *Reagents and conditions:* i) allylamine, neat, RT, 5 days.

The succinate derivative **23** was cyclised to *N*-allyl (*S*)-benzylsuccinimide **25** *via* the two-step procedure described above. Treatment of the succinate derivative **23** with TFA for 1 hour afforded the half acid **24** which was subsequently cyclised with 1,1′-carbonyldiimidazole in dichloromethane at room temperature. Purification by chromatography on silica gel afforded **25** in good yield and as a colourless oil. A ^{1}H NMR (300 MHz, $CDCl_3$) chiral shift experiment with Eu(hfc)$_3$ showed the ee of **25** to be >98%, Scheme 11.

In summary, a general route to chiral amides through the efficient, non-racemising, cleavage of *N*-acyl side chains from the 'Quat' chiral auxiliary using *N*-centred nucleophiles has been developed. The method works particularly well for unhindered primary amines and simply requires the mixing of the acyl donor with an excess (6 eq.) of amine at room temperature. Ammonia, as a solution in methanol at room temperature, can also be used in the reaction and provides a rapid route into the versatile parent amides. For more hindered amines the cleavage can be performed using the appropriate aluminium amides in dichloromethane or toluene. In these cases, the reaction times are dramatically reduced from days to hours. The utility of the method was then illustrated by conversion of (*S*)-2-phenylmethylpropanamide (*S*)-**4** to (*S*)-(+)-amphetamine through a stereospecific Hofman type degradation using a hypervalent iodine reagent, and by the



Scheme 11 *Reagents and conditions:* i) TFA, RT; ii) CDI (1.5 eq.), CH_2Cl_2, RT, overnight.

preparation of a range of succinamide and succinimide derivatives.

Experimental

Optical rotations were recorded using a Perkin-Elmer 241 which has a thermally jacketed 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were obtained by the Dyson Perrins analytical department using a Carla Erba 1106 analyser. Melting points were recorded using a Gallenkamp hot stage apparatus and are uncorrected. Infra-red spectra were obtained using a Perkin–Elmer 1750 spectrophotometer; solid samples as KBr discs and liquid samples as a thin film between sodium chloride plates. NMR spectra were recorded using either a Bruker AM500 (^{1}H; 500.13 MHz and ^{13}C; 125.8 MHz), WH 300 (^{1}H; 300.13 MHz), AM200 (^{1}H; 200 MHz and ^{13}C; 50.3 MHz) or Varian Gemini 200 (^{1}H; 200 MHz and ^{13}C; 50.32 MHz). All spectra were recorded using deuteriochloroform as solvent and internally referenced to residual protiochloroform (δ_H 7.27 and δ_C 77.0) unless otherwise stated. ^{1}H NMR spectra were run on a Bruker WH 300 unless otherwise stated. ^{13}C NMR were obtained with DEPT editing or assigned by analogy with spectra so recorded. All chemical shifts are given in parts per million relative to tetramethylsilane (δ_H 0.00) and coupling constants (J) are given in Hertz. Mass spectra were obtained in the Dyson Perrins analytical department using chemical ionisation (CI) or electronic ionisation (EI) on a VG MASSLAB VG 20–250 or on a Open Linx Micromass Platform 1 using APCI$^+$ or APCI$^-$. High resolution mass spectra were recorded using chemical ionisation (CI) on a VG-AutoSpec Instrument. Flash chromatography was carried out using silica gel (Kieselgel 60). Tetrahydrofuran was distilled from sodium benzophenone ketyl. Acetonitrile and dichloromethane were heated under reflux for 1 hour over calcium hydride prior to distillation. Methanol was distilled from glass. Petroleum ether refers to that fraction of petroleum ether boiling between 40 and 60 °C and was redistilled before use. All other solvents were used as received. Reactions were performed under an atmosphere of dry nitrogen unless otherwise stated.

Preparation of (5*R*)-1-(1′-oxopropyl)-3,3,5-trimethylpyrrolidin-2-one (*R*)-2 [23]

Butyllithium (26.3 ml, 39.4 mmol) was slowly added to a stirred solution of pyrrolidinone (*R*)-**1** (5.000 g, 39.37 mmol) in THF (120 ml) at −78 °C under a nitrogen atmosphere. Stirring was maintained at this temperature for a further 15 minutes before freshly distilled propionyl chloride (3.825 g, 41.34 mmol) was added dropwise *via* syringe. The reaction mixture was slowly warmed to room temperature (15 minutes), quenched with saturated aqueous ammonium chloride solution (~10 ml) and concentrated *in vacuo*. The residual material was partitioned between dichloromethane (80 ml) and distilled water (80 ml), and further extracted with dichloromethane (2 × 80 ml). The combined organic portions were washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield a crude yellow oil. Purification by silica gel chromatography [petroleum ether–diethyl ether (7 : 1)] afforded the title compound (*R*)-**2** as a colourless oil (6.87 g, 95%); $[\alpha]_D^{23}$ −101.0 (*c* 0.50, $CHCl_3$); lit.[23] $[\alpha]_D^{23}$ −101.0 (*c* 0.5, $CHCl_3$); δ_H 4.29–4.18 (1H, m, C*H*CH$_3$), 3.01–2.78 (2H, m, C*H*$_2$CH$_3$), 2.10 (1H, dd, *J* 13.3 and 8.5, C*H*$_2$CH), 1.56 (1H, dd, *J* 13.1 and 5.2, C*H*$_2$CH), 1.36 (3H, d, *J* 6.4, CHC*H*$_3$), 1.26 [3H, s, C(C*H*$_3$)$_2$], 1.17 [3H, s, C(C*H*$_3$)$_2$], 1.12 (3H, t, *J* 7.3, CH$_2$C*H*$_3$).

Preparation of (2′*S*,5*R*)-1-(1′oxo-2′-phenylmethylpropyl)-3,3,5-trimethylpyrrolidin-2-one 3 [23]

To a stirred solution of diisopropylamine (0.93 ml, 6.61 mmol) in THF (30 ml) at −78 °C was added butyllithium (4.02 ml, 6.31 mmol) *via* syringe. The resultant colourless solution was stirred at −78 °C (5 minutes), slowly warmed to 0 °C (10 minutes) and subsequently recooled to −78 °C.

A solution of (*R*)-**2** (1.100 g, 6.01 mmol) in THF (5 ml) was then added dropwise *via* cannula to the lithium amide solution. Stirring was maintained at −78 °C for 1 hour before benzyl bromide was added neat *via* syringe. The reaction mixture was slowly warmed to room temperature overnight, quenched with saturated aqueous ammonium chloride solution (5 ml) and concentrated *in vacuo*. The residual material was partitioned between diethyl ether (50 ml) and brine (30 ml), and further extracted with diethyl ether (2 × 50 ml). The combined organic portions were dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield a crude yellow oil. Inspection of the crude ^{1}H NMR spectrum (300 MHz, $CDCl_3$) indicated that the major reaction product had formed with a diastereomeric excess of >96%. Purification by silica gel chromatography [petroleum ether–diethyl ether (9 : 1)] afforded the title compound **3** as a mixture of diastereoisomers (>96% de) and as a colourless oil (1.408 g, 86%); $[\alpha]_D^{23}$ −20.3 (*c* 0.60, $CHCl_3$); lit.[23] $[\alpha]_D^{23}$ −20.0 (*c* 0.6, $CHCl_3$); δ_H 7.28–7.14 (5H, m, Ph), 4.27–4.16 (1H, m, CHN), 4.15–4.03 (1H, m, CHCO), 3.05 (1H, dd, *J* 13.3 and 6.9, PhC*H*$_2$), 2.60 (1H, dd, *J* 13.2 and 8.1, PhC*H*$_2$), 2.05 (1H, dd, *J* 12.9 and 8.4, CH$_2$CHN), 1.47 (1H, dd, *J* 13.1 and 5.5, C*H*$_2$CHN), 1.21 [3H, s, (C*H*$_3$)$_2$C], 1.17 (3H, d, *J* 6.1, CHC*H*$_3$), 1.17 [3H, s, (C*H*$_3$)$_2$C], 1.11 (3H, d, *J* 6.7, CHC*H*$_3$); δ_C 181.0 (N*C*=O), 178.7 (CH*C*=O), 139.7 (Ph: C$_{ipso}$), 129.5 and 128.4 (Ph), 126.3 (Ph: C$_{para}$), 49.9 (*C*HN), 42.0 [(CH$_3$)$_2$*C*], 40.9 (*C*HCO), 40.4 and 40.2 (CH$_2$), 26.0 [C(*C*H$_3$)$_2$], 25.9 [C(*C*H$_3$)$_2$], 20.9 and 15.8 (CH*C*H$_3$).

Preparation of (*S*)-2-phenylmethylpropanamide (*S*)-4

Compound **3** (0.200 g, 0.733 mmol) was dissolved in freshly distilled methanol (5 ml) and subsequently cooled to 0 °C with stirring. Gaseous ammonia was then slowly bubbled through the chilled solution *via* cannula for 2 hours. On warming to room temperature, the volatiles were removed *in vacuo* to afford a pale yellow oil which solidified on standing. Trituration of this solid residue with *n*-pentane (3 × 20 ml) afforded the title compound (*S*)-**4** (0.081 g, 68%) as colourless crystals. Concentration of the mother liquor *in vacuo* afforded a pale yellow oil. Inspection of the ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the mother liquor indicated the presence of (*R*)-**1**, (*S*)-**4** and (*S*)-**5** [tentatively assigned on the basis of a singlet resonance at δ3.63 (OC*H*$_3$)] in the relative ratios 80 : 8 : 12 respectively. Attempted purification of the triturand by chromatography i) failed to isolate methyl ester (*S*)-**5** and ii) failed to separate the polar amidic components. Accordingly, the reaction yields for (*R*)-**1** and (*S*)-**4** were approximated to be >80% and <20%, respectively.

(*S*)-**4**; mp 114–115 °C; lit.[10] 113–114 °C; $[\alpha]_D^{24}$ +55.4 (*c* 0.675, EtOH); lit.[10] $[\alpha]_D^{21}$ +53.1 (*c* 2.5, EtOH) (Found: C, 73.79; H, 8.08; N, 8.31. $C_{10}H_{13}NO$ requires C, 73.59; H, 8.03; N, 8.58%); δ_H 7.31–7.17 (5H, m, Ph), 5.64 (1H, br s, N*H*), 5.33 (1H, br s, N*H*), 2.99 (1H, dd, *J* 13.4 and 7.8, PhCH_2), 2.67 (1H, dd, *J* 13.4 and 6.8, PhCH_2), 2.59–2.47 (1H, m, C*H*CH_3), 1.19 (3H, d, *J* 6.8, CHCH_3); *m*/*z* (APCI$^+$) 164 (100%, MH^+), 119 (95%, $M^+ - CH_2NO$).

A ^{1}H NMR (300 MHz, $CDCl_3$) chiral shift experiment with Eu(hfc)$_3$ showed the ee of (*S*)-**4** to be >98%.

Preparation of (*S*)-(+)-amphetamine HCl (*S*)-6

To a stirred solution of amide (*S*)-**4** (0.050 g, 0.307 mmol) in acetonitrile–distilled water (1 : 1, 2 ml) at room temperature was added [bis(trifluoroacetoxy)iodo]benzene (0.198 g, 0.460 mmol) in one portion. The reaction mixture was stirred at room temperature for 5 hours and was then quenched by the addition of aqueous hydrochloric acid (1–M, 10 ml). The aqueous layer was extracted with diethyl ether (2 × 20 ml) and concentrated *in vacuo* to yield a white solid. Recrystallisation of this material from ethanol–diethyl ether afforded the title compound (*S*)-**6** as white needles (0.048 g, 91%); mp 156–157 °C; lit.[15] mp 156 °C; $[\alpha]_D^{21}$ +25.9 (*c* 1.00, H_2O); lit.[16] $[\alpha]_D^{20}$ +27.5 (*c* 1.00, H_2O); δ_H (lit.[16]) 8.43 (3H, br s, NH_3), 7.33–7.21 (5H, m, Ph), 3.66–3.56 (1H, m, C*H*N), 3.28 (1H, dd, *J* 13.3 and 5.0, PhCH_2), 2.86 (1H, dd, *J* 13.2 and 9.4, PhCH_2), 1.38 (3H, d, *J* 6.4, CHCH_3); *m*/*z* (APCI$^+$) 136 (100%, MH^+), 119 (80%, $MH^+ - NH_3$).

The enantiomeric excess of (*S*)-**6** was measured as being >98% by derivatisation as the Mosher's amide.

Preparation of (*S*)-*N*-vinylmethyl-2-phenylmethylpropanamide (*S*)-7

To neat **3** (0.100 g, 0.366 mmol) at room temperature was added neat allylamine (0.125 g, 0.366 mmol) *via* pipette. The reaction mixture was stirred at room temperature for 36 hours before the excess amine was removed *in vacuo* to afford a pale yellow oil. This material was purified by flash chromatography on silica gel [diethyl ether (100%) then ethyl acetate (100%)] eluting first the title compound (*S*)-**7** (0.073 g, 98%) as a colourless oil which crystallised on standing, followed by the more polar pyrrolidinone (*R*)-**1** (0.045 g, 97%) as colourless crystals.

(*S*)-**7**; mp 32–33 °C; $[\alpha]_D^{24}$ +59.0 (*c* 0.93, $CHCl_3$) (Found: C, 76.62; H, 8.53; N, 6.86. $C_{13}H_{17}NO$ requires C, 76.81; H, 8.43; N, 6.89%); ν_{max}(film)/cm^{-1} 3270br s (N–H), 1639s and 1560s (NC=O); δ_H 7.37–7.17 (5H, m, Ph), 5.75 (1H, ddt, *J* 17.0, 10.6 and 5.6, CH_2=C*H*), 5.35 (1H, br s, N*H*), 5.10 (1H, d, *J* 10.6, CH_2=CH), 5.05 (1H, d, *J* 17.4, CH_2=CH), 3.90 (1H, dd, *J* 15.7 and 5.7, CH_2N), 3.81 (1H, dd, *J* 15.6 and 5.6, CH_2N), 3.05 (1H, dd, *J* 13.4 and 8.4, PhCH_2), 2.76 (1H, dd, *J* 13.4 and 6.4, PhCH_2), 2.57–2.46 (1H, m, C*H*CH_3), 1.27 (3H, d, *J* 6.8, CHCH_3); δ_C (50 MHz) 175.6 (*C*=O), 139.9 (Ph: C_{ipso}), 134.2 (CH_2=*C*H), 129.0 and 128.4 (Ph: C), 126.2 (Ph: C_{para}), 116.0 (*C*H_2=CH), 43.7 (*C*HCH_3), 41.6 (*C*H_2N), 40.4 (Ph*C*H_2), 17.7 (CH*C*H_3); *m*/*z* (APCI$^+$) 204 (100%, MH^+).

A ^{1}H NMR (300 MHz, $CDCl_3$) chiral shift experiment with Eu(hfc)$_3$ showed the ee of (*S*)-**7** to be >96%.

Preparation of (2*S*)-*N*-phenylmethyl-2-phenylmethylpropanamide (*S*)-8

To **3** (0.100 g, 0.366 mmol) at room temperature was added neat benzylamine (0.235 g, 2.20 mmol) *via* pipette. The reaction mixture was stirred at room temperature for 36 hours and then partitioned between dichloromethane (30 ml) and aqueous hydrochloric acid (10%, 30 ml) and further extracted with dichloromethane (2 × 30 ml). The combined organic portions were washed with brine (20 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. This material was purified by flash chromatography on silica gel [diethyl ether–petroleum ether (1 : 1) then ethyl acetate (100%)] eluting first the less polar (*S*)-**8** (0.089 g, 96%) followed by the more polar (*R*)-**1** (0.043 g, 92%) as colourless solids.

(*S*)-**8**; mp 83–84 °C; $[\alpha]_D^{24}$ +52.3 (*c* 1.24, $CHCl_3$) (Found: C, 80.60; H, 7.74; N, 5.50. $C_{17}H_{19}NO$ requires C, 80.60; H, 7.56; N, 5.53%); ν_{max}(KBr)/cm^{-1} 3276br s (N–H), 1634s and 1549s (NC=O); δ_H 7.29–7.02 (10H, m, Ph), 5.46 (1H, br s, N*H*), 4.40 (1H, dd, *J* 14.7 and 6.0, CH_2N), 4.28 (1H, dd, *J* 14.8 and 5.5, CH_2N), 2.99 (1H, dd, *J* 13.4 and 8.8, PhCH_2), 2.71 (1H, dd, *J* 13.4 and 6.2, PhCH_2), 2.46 (1H, m, C*H*CH_3), 1.23 (3H, d, *J* 6.8, CHCH_3); δ_C (50 MHz) 175.4 (*C*=O), 139.9 (Ph: C_{ipso}), 129.0, 128.6, 128.4, 127.6, 127.3 and 126.3 (Ph), 44.0 (*C*HCH_3), 43.3 (*C*H_2N), 40.5 (Ph*C*H_2), 17.9 (CH*C*H_3); *m*/*z* (APCI$^+$) 254 (100%, MH^+).

Preparation of (2*S*)-*N*-*tert*-butoxycarbonylmethyl-2-phenylmethylpropanamide (*S*)-9

To **3** (0.035 g, 0.128 mmol) at room temperature was added neat *tert*-butyl glycinate (0.097 g; 0.740 mmol) *via* pipette. The reaction mixture was stirred at room temperature for 120 hours before the excess amine was removed *in vacuo* to afford a pale yellow oil. This material was purified by flash chromatography on silica gel [diethyl ether–petroleum ether (1 : 1) then ethyl acetate (100%)] eluting first the less polar (*S*)-**9** (0.035 g, 99%) as a colourless oil followed by the more polar (*R*)-**1** (0.016 g, 98%) as a colourless solid.

(*S*)-**9**; $[\alpha]_D^{21}$ +46.0 (*c* 1.75, $CHCl_3$) (Found: C, 69.09; H, 8.97; N, 4.90. $C_{16}H_{23}NO_3$ requires C, 69.29; H, 8.36; N, 5.05%); ν_{max}(film)/cm^{-1} 2978s and 2934s (N–H), 1748s (OC=O), 1651s (NC=O) and 1538s; δ_H 7.26–7.13 (5H, m, Ph), 6.01 (1H, br s, N*H*), 3.92 (1H, dd, *J* 18.3 and 5.4, CH_2CO), 3.76 (1H, dd, *J* 18.3 and 4.6, CH_2CO), 3.00 (1H, dd, *J* 13.2 and 7.1, PhCH_2), 2.64 (1H, dd, *J* 13.2 and 7.5, PhCH_2), 2.52 (1H, m, C*H*CH_3), 1.43 [9H, s, C(CH_3)$_3$], 1.15 (3H, d, *J* 6.7, CHCH_3); δ_C (50 MHz) 176.0 (N*C*=O), 169.4 (O*C*=O), 139.9 (Ph: C_{ipso}), 129.1 and 128.6 (Ph: C), 126.4 (Ph: C_{para}), 82.3 [*C*(CH$_3$)$_3$], 43.3 (*C*HCH_3), 41.8 (N*C*H_2), 40.1 (Ph*C*H_2), 27.9 [C(*C*H$_3$)$_3$], 17.2 (CH*C*H_3); *m*/*z* (APCI$^+$) 300 (7%, MNa^+), 278 (3%, MH^+), 222 (92%, $MH^+ - C_4H_8$), 147 (79%), 119 (100%, $C_9H_{11}^+$); [Found (CI, NH_3): MH^+, 278.17459. $C_{16}H_{24}NO_3$ MH^+ requires, 278.17562].

Preparation of (4*R*)-4-{[(2*S*)-2-methyl-3-phenylpropanoyl]-amino}-2,2-dimethyl-*N*-(vinylmethyl)pentanamide 10

To a stirred solution of allylamine (0.061 g, 1.10 mmol) in dichloromethane (1 ml) at room temperature was added cautiously trimethylaluminium (0.55 ml, 1.10 mmol) *via* syringe. The resultant colourless solution was stirred at room temperature for a further 15 minutes (effervescence ceased after 5 minutes).

A solution of **3** (0.100 g, 0.366 mmol) in dichloromethane (1 ml) was then added dropwise *via* pipette to the aluminium amide solution. The reaction mixture was stirred under reflux for 4 hours, cooled to room temperature and quenched with distilled water (5 ml). The aqueous layer was acidified to pH 1 with concentrated sulfuric acid and subsequently extracted with dichloromethane (3 × 20 ml). The combined organic portions were washed with brine (20 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield a crude yellow oil. This material was purified by flash chromatography on silica gel [diethyl ether–petroleum ether (1 : 1) then ethyl acetate (100%)] eluting first the amide (*S*)-**7** (0.057 g, 77%) as a colourless oil, then the more polar endocyclic cleavage product **10** (0.024 g, 20%) as a colourless oil, followed by the more polar pyrrolidinone (*R*)-**1** (0.034 g, 73%) as a colourless solid.

10; $[\alpha]_D^{24}$ +62.7 (*c* 0.675, $CHCl_3$) (Found: C, 73.35; H, 9.55; N, 8.32. $C_{20}H_{30}N_2O_2$ requires C, 72.69; H, 9.15; N, 8.48%); ν_{max}(film)/cm^{-1} 3316br s (N–H), 1641br s and 1534br s (NC=O); δ_H (500 MHz, $CDCl_3$) 7.47–7.19 (5H, m, Ph), 5.90 (1H, br t,

J 4.7, CH_2NH), 5.80 (1H, ddt, *J* 17.1, 10.3 and 5.7, $CH_2{=}CH$), 5.57 (1H, br d, *J* 8.1, CHN*H*), 5.18–5.12 (2H, m, $CH_2{=}CH$), 4.00–3.92 (2H, m, CH_2N), 3.70–3.64 (1H, m, C*H*N), 2.88 (1H, dd, *J* 13.4 and 8.4, $PhCH_2$), 2.61 (1H, dd, *J* 13.4 and 6.8, $PhCH_2$), 2.31–2.26 (1H, m, C*H*CO), 2.10 (1H, dd, *J* 14.4 and 11.1, CH_2CHN), 1.26 (1H, dd, *J* 14.4 and 3.7, CH_2CHN), 1.19 [3H, s, $C(CH_3)_2$], 1.16 [3H, s, $C(CH_3)_2$], 1.09 (3H, d, *J* 6.8, $CHCH_3$), 0.87 (3H, d, *J* 6.4, $CHCH_3$); δ_C (125 MHz) 178.4 and 175.6 (*C*=O), 139.8 (Ph: C_{ipso}), 133.9 ($CH_2{=}CH$), 129.0 and 128.3 (Ph: C), 126.2 (Ph: C_{para}), 116.6 ($CH_2{=}CH$), 45.4 (CH_2CHN), 43.7 ($CHCH_3$), 42.4 (*C*HN), 42.1 (CH_2N), 40.8 [$C(CH_3)_2$], 40.6 ($PhCH_2$), 29.5 (CH_3CHN), 23.1 and 22.3 [$C(CH_3)_2$], 17.3 ($CHCH_3$); *m*/*z* ($APCI^+$) 353 (15%, MNa^+), 331 (100%, MH^+), 168 (6%), 128 (10%); [Found (CI, NH_3): MH^+, 331.23917. $C_{20}H_{31}N_2O_2$ MH^+ requires, 331.23855].

A ^1H NMR (300 MHz, $CDCl_3$) chiral shift experiment with $Eu(hfc)_3$ showed the ee of (*S*)-**7** to be >96%.

Preparation of (2*S*)-*N*-methoxy-*N*-methyl-2-phenylmethylpropionamide (*S*)-11

To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (0.098 g, 1.10 mmol) in dichloromethane (1 ml) at 0 °C was added cautiously trimethylaluminium (0.55 ml, 1.10 mmol) *via* syringe. The resultant colourless solution (effervescence ceased after 5 minutes) was stirred at 0 °C for 15 minutes and room temperature for 45 minutes.

A solution of **3** (0.137 g, 0.50 mmol) in dichloromethane (0.5 ml) was then added dropwise *via* cannula to the aluminium amide solution. The reaction mixture was stirred at room temperature for 22 hours and under reflux for 3 hours, cooled to 0 °C and subsequently quenched with aqueous sulfuric acid (1 M). The acidic (pH 1) aqueous layer was diluted with distilled water (20 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic portions were washed with brine (20 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield a crude yellow oil. This material was purified by flash chromatography on silica gel [ethyl acetate–petroleum ether (1 : 2) then ethyl acetate (100%)] eluting first the less polar title compound (*S*)-**11** (0.060 g, 79%) as a colourless oil followed by the more polar pyrrolidinone (*R*)-**1** (0.043 g, 93%) as a colourless solid.

11; $[a]_D^{22}$ +60.7 (*c* 0.755, $CHCl_3$) (Found: C, 69.55; H, 8.59; N, 6.75. $C_{12}H_{17}NO_2$ requires C, 69.54; H, 8.27; N, 6.76%); ν_{max}(film)/cm^{-1} 1662s (NC=O); δ_H 7.27–7.16 (5H, m, Ph), 3.47 (3H, s, CH_3O), 3.13 (4H, br s, CH_3N and $CHCH_3$), 3.03 (1H, dd, *J* 13.2 and 7.8, $PhCH_2$), 2.61 (1H, dd, *J* 13.1 and 6.8, $PhCH_2$), 1.15 (3H, d, *J* 6.7, $CHCH_3$); δ_C (50 MHz) 177.4 (*C*=O), 140.4 (Ph: C_{ipso}), 129.3 and 128.5 (Ph: C), 126.3 (Ph: C_{para}), 61.3 (CH_3O), 39.8 ($PhCH_2$), 37.5 ($CHCH_3$), 32.1 (CH_3N), 17.2 ($CHCH_3$); *m*/*z* ($APCI^+$) 208 (100%, MH^+), 119 (20%, $C_9H_{11}^+$).

Preparation of (2*S*)-*N*-vinylmethyl-2-[(*tert*-butoxycarbonyl)-methyl]propionamide (*S*)-13

To neat **12** (0.150 g, 0.505 mmol) at room temperature was added neat allylamine (0.173 g, 3.028 mmol) *via* pipette. The reaction mixture was stirred at room temperature for 48 hours before the excess amine was removed *in vacuo* to afford a pale yellow oil. This material was purified by flash chromatography on silica gel [diethyl ether–petroleum ether (1 : 1) then ethyl acetate (100%)] eluting first the title compound (*S*)-**13** (0.109 g, 95%) as a colourless oil followed by the more polar pyrrolidinone (*R*)-**1** (0.062 g, 97%) as colourless crystals.

(*S*)-**13**; $[a]_D^{23}$ +0.6 (*c* 0.67, $CHCl_3$) (Found: C, 63.04; H, 9.69; N, 6.09. $C_{12}H_{21}NO_3$ requires C, 63.41; H, 9.31; N, 6.16%); ν_{max}(film)/cm^{-1} 3301br s (N–H), 1732s (OC=O), 1652s (NC=O) and 1547s; δ_H 5.90–5.75 (2H, m, N*H* and $CH{=}CH_2$), 5.17 (1H, d, *J* 17.1, $CH{=}CH_2$), 5.11 (1H, d, *J* 10.2, $CH{=}CH_2$), 3.88–3.84 (2H, m, CH_2N), 2.74–2.61 (2H, m, $CHCH_3$ and CH_2CO_2), 2.34–2.24 (1H, m, CH_2CO_2), 1.42 [9H, s, $C(CH_3)_3$], 1.17 (3H, d, *J* 6.5, $CHCH_3$); δ_C 175.4 (N*C*=O), 172.1 (O*C*=O), 134.4 ($CH{=}CH_2$), 116.1 ($CH{=}CH_2$), 80.7 [$C(CH_3)_3$], 41.6 (CH_2N), 39.2 (CH_2CO_2), 36.9 ($CHCH_3$), 27.8 [$C(CH_3)_3$], 17.5 ($CHCH_3$); *m*/*z* ($APCI^+$) 250 (10%, MNa^+), 172 (60%, $MH^+ - C_4H_8$), 154 (100%, $MH^+ - C_4H_{10}O$).

Preparation of (2*S*)-*N*-phenylmethyl-2-[(*tert*-butoxycarbonyl)-methyl]propionamide (*S*)-14

To **12** (0.150 g, 0.505 mmol) at room temperature was added neat benzylamine (0.324 g, 3.028 mmol) *via* pipette. The reaction mixture was stirred at room temperature for 48 hours and then partitioned between dichloromethane (30 ml) and aqueous hydrochloric acid (10%, 30 ml) and further extracted with dichloromethane (2 × 30 ml). The combined organic portions were washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. This material was purified by flash chromatography on silica gel [diethyl ether–petroleum ether (1 : 1) then ethyl acetate (100%)] eluting first the less polar title compound (*S*)-**14** (0.134 g, 96%) as a colourless oil which crystallised on standing, followed by the more polar pyrrolidinone (*R*)-**1** (0.059 g, 92%) as a colourless solid.

(*S*)-**14**; mp 45–46 °C; $[a]_D^{23}$ −7.1 (*c* 0.68, $CHCl_3$) (Found: C, 69.41; H, 8.47; N, 4.84. $C_{16}H_{23}NO_3$ requires C, 69.29; H, 8.36; N, 5.05%); ν_{max}(film)/cm^{-1} 3302br s (N–H), 1729s (OC=O), 1651s (NC=O) and 1546s; δ_H 7.34–7.22 (5H, m, Ph), 6.16 (1H, br s, N*H*), 4.49–4.36 (2H, m, $PhCH_2$), 2.76–2.64 (2H, m, $CHCH_3$ and CH_2CO_2), 2.35–2.25 (1H, m, CH_2CO_2), 1.41 (9H, s, $C(CH_3)_3$), 1.19 (3H, d, *J* 6.5, $CHCH_3$); δ_C (50 MHz) 175.5 (N*C*=O), 172.2 (O*C*=O), 138.8 (Ph: C_{ipso}), 128.7, 127.8 and 127.4 (Ph: C), 80.7 [$C(CH_3)_3$], 43.3 ($PhCH_3$), 39.3 (CH_2CO_2), 37.0 ($CHCH_3$), 27.9 [$C(CH_3)_3$], 17.6 ($CHCH_3$); *m*/*z* ($APCI^+$) 300 (12%, MNa^+), 222 (100%, $MH^+ - C_4H_8$).

Preparation of (2*S*)-*N*-(4-methoxyphenylmethyl)-2-[(*tert*-butoxycarbonyl)methyl]propionamide (*S*)-15

To **12** (0.150 g, 0.505 mmol) at room temperature was added neat *p*-methoxybenzylamine (0.415 g, 3.029 mmol) *via* pipette. The reaction mixture was stirred at room temperature for 48 hours and then partitioned between dichloromethane (30 ml) and aqueous hydrochloric acid (10%, 30 ml) and further extracted with dichloromethane (2 × 30 ml). The combined organic portions were washed with brine (20 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. This material was purified by flash chromatography on silica gel [diethyl ether–petroleum ether (1 : 1) then ethyl acetate (100%)] eluting first the less polar title compound (*S*)-**15** (0.139 g, 89%) as a colourless oil followed by the more polar pyrrolidinone (*R*)-**1** (0.060 g, 94%) as a colourless solid.

(*S*)-**15**; $[a]_D^{23}$ −8.5 (*c* 0.685, $CHCl_3$); ν_{max}(film)/cm^{-1} 3303br s (N–H), 1732s (OC=O), 1652s (NC=O) and 1544s; δ_H 7.26–7.12 (2H, m, Ar), 6.82–6.78 (2H, m, Ar), 6.30 (1H, br s, N*H*), 4.33 (1H, dd, *J* 15.1 and 5.8, CH_2N), 4.28 (1H, dd, *J* 15.1 and 9.4, CH_2N), 3.74 (3H, s, CH_3O), 2.71–2.59 (2H, m, $CHCH_3$ and CH_2CO_2), 2.30–2.20 (1H, m, CH_2CO_2), 1.38 [9H, s, $C(CH_3)_3$], 1.14 (3H, d, *J* 6.5, $CHCH_3$); δ_C (50 MHz) 175.4 (N*C*=O), 172.2 (O*C*=O), 159.1 and 130.8 (Ph: C_{ipso}), 129.2 and 114.1 (Ph: C), 80.8 [$C(CH_3)_3$], 55.2 (CH_3O), 42.8 (CH_2N), 39.3 (CH_2CO_2), 37.0 ($CHCH_3$), 27.9 [$C(CH_3)_3$], 17.7 ($CHCH_3$); *m*/*z* ($APCI^+$) 330 (10%, MNa^+), 308 (16%, MH^+), 252 (100%, $MH^+ - C_4H_8$), 136 (6%), 121 (17%); [Found (CI, NH_3): MH^+, 308.18633. $C_{17}H_{25}NO_4$ MH^+ requires, 308.18618].

Preparation of (3*S*)-3-methyl-1-vinylmethylpyrrolidine-2,5-dione (*S*)-19[22]

To (*S*)-**13** (0.057 g, 0.251 mmol) in a 5 ml round bottom flask was added TFA (3 ml) neat *via* pipette. The mixture was left

to stand at room temperature for 1 hour before the volatiles were removed *in vacuo*. Toluene (3 ml) was then added to the oily residue and subsequently removed *in vacuo* to afford the intermediate acid (*S*)-**16** as a colourless oil [*m*/*z* (APCI$^-$) 170 (M − H$^+$)]. The intermediate acid was used directly in the next step without further purification or characterisation.

To this material was added 1,1′-carbonyldiimidazole (0.061 g, 0.377 mmol) and the mixture was subsequently dissolved in dichloromethane (1 ml) and stirred at room temperature for 16 hours. The reaction mixture was diluted with dichloromethane (30 ml), washed with aqueous hydrochloric acid (0.1 M, 2 × 30 ml) then brine (30 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. Purification by flash chromatography on silica gel [diethyl ether–petroleum ether (1 : 1)] afforded the title compound (*S*)-**19** as a colourless oil (0.029 g, 76%); $[a]_D^{23}$ −17.2 (*c* 1.0, $CHCl_3$); lit.[22] for the (*R*)-enantiomer (70% ee), $[a]_D^{22}$ +13.4 (*c* 0.88, $CHCl_3$); δ_H 5.77 (1H, ddt, *J* 17.0, 10.4 and 5.6, CH_2=C*H*), 5.22–5.15 (2H, m, CH_2=CH), 4.08 (2H, d, *J* 5.9, CH_2N), 2.98–2.80 (2H, m, C*H*CH_3 and CH_2CO), 2.32 (1H, dd, *J* 17.0 and 3.6, CH_2CO), 1.34 (3H, d, *J* 7.0, CHCH_3).

A ^{1}H NMR (300 MHz, $CDCl_3$) chiral shift experiment with Eu(hfc)$_3$ showed the ee of (*S*)-**19** to be >98%.

Preparation of (3*S*)-3-methyl-1-phenylmethylpyrrolidine-2,5-dione (*S*)-20[22]

To (*S*)-**14** (0.047 g, 0.170 mmol) in a 5 ml round bottom flask was added TFA (3 ml) neat *via* pipette. The mixture was left to stand at room temperature for 1 hour before the volatiles were removed *in vacuo*. Toluene (3 ml) was then added to the oily residue and subsequently removed *in vacuo* to afford the intermediate acid (*S*)-**17** as a colourless oil which crystallised on standing [*m*/*z* (APCI$^-$) 220 (M − H$^+$)]. The intermediate acid was used directly in the next step without further purification or characterisation.

To this material was added 1,1′-carbonyldiimidazole (0.041 g, 0.254 mmol) and the mixture was subsequently dissolved in dichloromethane (1 ml) and stirred at room temperature for 14 hours. The reaction mixture was diluted with dichloromethane (30 ml), washed with aqueous hydrochloric acid (0.1 M, 2 × 30 ml) then brine (30 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. Purification by flash chromatography on silica gel [diethyl ether–petroleum ether (1 : 1)] afforded the title compound (*S*)-**20** as a colourless oil (0.030 g, 88%); $[a]_D^{23}$ −19.6 (*c* 1.52, $CHCl_3$); lit.[22] for the (*R*)-enantiomer (80% ee), $[a]_D^{22}$ +14.4 (*c* 1.39, $CHCl_3$); δ_H 7.39–7.25 (5H, m, Ph), 4.65 (2H, s, CH_2N), 2.97–2.80 (2H, m, C*H*CH_3 and CH_2CO), 2.38–2.26 (1H, m, CH_2CO), 1.33 (3H, d, *J* 7.1, CHCH_3).

Preparation of (3*S*)-3-methyl-1-(4-methoxyphenylmethyl)-pyrrolidine-2,5-dione (*S*)-21

To (*S*)-**15** (0.058 g, 0.189 mmol) in a 5 ml round bottom flask was added TFA (3 ml) neat *via* pipette. The mixture was left to stand at room temperature for 1 hour before the volatiles were removed *in vacuo*. Toluene (3 ml) was then added to the oily residue and subsequently removed *in vacuo* to afford the intermediate acid (*S*)-**18** as a colourless oil [*m*/*z* (APCI$^-$) 250 (M − H$^+$)]. The intermediate acid was used directly in the next step without further purification or characterisation.

To this material was added 1,1′-carbonyldiimidazole (0.046 g, 0.283 mmol) and the mixture was subsequently dissolved in dichloromethane (1 ml) and stirred at room temperature for 16 hours. The reaction mixture was diluted with dichloromethane (30 ml), washed with aqueous hydrochloric acid (0.1 M, 2 × 30 ml) then brine (30 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. Purification by flash chromatography on silica gel [diethyl ether–petroleum ether (1 : 1)] afforded the title compound (*S*)-**21** as a colourless oil (0.037 g, 83%); $[a]_D^{21}$ −17.3 (*c* 1.10, $CHCl_3$) (Found: C, 66.95; H, 6.47; N, 5.96. $C_{13}H_{15}NO_3$ requires C, 66.94; H, 6.48; N, 6.00%); ν_{max}(film)/cm^{-1} 1761s and 1693s (C=O); δ_H 7.31–7.26 (2H, m, Ar), 6.81–6.76 (2H, m, Ar), 4.53 (2H, s, ArCH_2), 3.73 (3H, s, CH_3O), 2.89–2.72 (2H, m, C*H*CH_3 and CH_2CO), 2.31–2.19 (1H, m, CH_2CO), 1.28 (3H, d, *J* 6.7, CHCH_3); δ_C (50 MHz) 180.6 and 176.5 (*C*=O), 159.5 (Ar: *C*OMe), 130.4 (Ar), 128.4 (Ar: C$_{ipso}$), 114.0 (Ar), 55.2 (*C*H_3O), 41.7 (Ar*C*H_2), 36.3 (*C*H_2CO), 34.6 (*C*HCH$_3$), 16.5 (CH*C*H_3); *m*/*z* (APCI$^+$) 251 (100%, MNH_4^+), 234 (60%, MH$^+$), 121 (10%).

Preparation of (2*S*)-*N*-vinylmethyl-2-[(*tert*-butoxycarbonyl)-methyl]-3-phenylpropionamide (*S*)-23

To solid **22** (0.150 g, 0.420 mmol) at room temperature was added neat allylamine (0.240 g, 4.21 mmol) *via* pipette. The homogeneous reaction mixture was stirred at room temperature for 5 days before the excess amine was removed *in vacuo* to afford a pale yellow oil. This material was purified by flash chromatography on silica gel [diethyl ether–petroleum ether (2 : 1) then ethyl acetate (100%)] eluting first the title compound (*S*)-**23** (0.107 g, 84%) as a colourless oil which crystallised on standing, followed by the more polar pyrrolidinone (*R*)-**1** (0.042 g, 79%) as colourless crystals. A small amount of (*S*)-**23** was recrystallised from diethyl ether–pentane for analysis.

(*S*)-**23**; $[a]_D^{21}$ −45.4 (*c* 0.59, $CHCl_3$) (Found: C, 71.62; H, 8.55; N, 4.53. $C_{18}H_{25}NO_3$ requires C, 71.26; H, 8.31; N, 4.62%); ν_{max}(KBr)/cm^{-1} 1730s (OC=O), 1652 (NC=O), 1637; δ_H 7.31–7.17 (5H, m, Ph), 5.65 (1H, ddt, *J* 17.0, 10.5 and 5.5, CH_2=C*H*), 5.52 (1H, br, N*H*), 5.02–4.95 (2H, m, CH_2=CH), 3.76 (2H, dd, *J* 5.5 and 5.6, CH_2N), 2.94 (1H, dd, *J* 11.9 and 7.1, PhCH_2), 2.83–2.66 (3H, m, PhCH_2, CH_2CO$_2$ and C*H*CO), 2.38 (1H, dd, *J* 15.9 and 3.4, CH_2CO$_2$), 1.42 [9H, s, C(CH_3)$_3$]; δ_C (50 MHz) 174.0 (N$_C$=O), 172.1 (O*C*=O), 139.3 (Ph: C$_{ipso}$), 134.3 (CH_2=*C*H), 129.2, 128.7 (Ph: C), 126.7 (Ph: C$_{para}$), 116.1 (*C*H_2=CH), 80.9 [*C*(CH$_3$)$_3$], 45.1 (*C*HCO), 41.6 (*C*H_2N), 38.4 and 37.5 (Ph*C*H_2 and *C*H_2CO$_2$), 27.9 [C(*C*H_3)$_3$]; *m*/*z* (APCI$^+$) 326 (6%, MNa$^+$), 304 (5%, MH$^+$), 248 (100%, MH$^+$ − C_4H_8), 230 (14%).

Preparation of (2*S*)-*N*-vinylmethyl-2-phenylmethylsuccinimide (*S*)-25

To (*S*)-**23** (0.050 g, 0.165 mmol) in a 5 ml round bottom flask was added TFA (3 ml) neat *via* pipette. The mixture was left to stand at room temperature for 1 hour before the volatiles were removed *in vacuo*. Toluene (3 ml) was then added to the oily residue and subsequently removed *in vacuo* to afford the intermediate acid (*S*)-**24** as a colourless oil [*m*/*z* (APCI$^-$) 246 (100%, M − H$^+$), 228 (5%)]. The intermediate acid was used directly in the next step without further purification or characterisation. To this material was added 1,1′-carbonyldiimidazole (0.040 g, 0.248 mmol) and the mixture was subsequently dissolved in dichloromethane (1 ml) and stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane (30 ml), washed with aqueous hydrochloric acid (0.1 M, 2 × 30 ml) then brine (30 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford a colourless oil. Purification by flash chromatography on silica gel [diethyl ether–petroleum ether (1 : 1)] afforded the title compound (*S*)-**25** as a colourless oil (0.033 g, 87%); $[a]_D^{23}$ +71.6 (*c* 0.70, $CHCl_3$) (Found: C, 72.83; H, 6.76; N, 6.87. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11%); ν_{max}(film)/cm^{-1} 1775s and 1698s (C=O); δ_H 7.31–7.13 (5H, m, Ph), 5.69 (1H, ddt, *J* 16.9, 10.5 and 5.8, CH_3=C*H*), 5.13–5.05 (2H, m, CH_3=CH), 4.04 (2H, d, *J* 5.8, CH_2N), 3.21–3.08 (2H, m, PhCH$_3$ and CHCO), 2.88 (1H, dd, *J* 12.9 and 8.0, PhCH_2), 2.68 (1H, dd, *J* 18.4 and 8.6, CH_2CO$_2$), 2.44 (1H, dd, *J* 18.3 and 4.6, CH_2CO$_2$); δ_C (50 MHz) 179.1 and 176.1 (*C*=O), 137.2 (Ph: C$_{ipso}$), 130.8 (CH_2=*C*H), 129.3 and 129.0 (Ph), 127.2 (Ph: C$_{para}$), 118.2 (*C*H_2=CH), 41.1 (*C*HCO), 40.7 (*C*H_2N), 36.3 and 33.1 (Ph*C*H_2 and *C*H_2CO$_2$); *m*/*z* (CI, NH$_3$)

247 (100%, MNH_4^+), 230 (55%, MH^+), 108 (9%), 91 (6%), 121 (10%); [Found (CI, NH_3): MH^+, 230.11768. $C_{14}H_{15}NO_2$ MH^+ requires, 230.11810].

A ^1H NMR (300 MHz, $CDCl_3$) chiral shift experiment with Eu(hfc)$_3$ showed the ee of (*S*)-**25** to be >98%.

Acknowledgements

We thank Oxford Asymmetry Ltd and the EPSRC for a CASE award (to D. J. D.).

References

1 For a recent review see P. Arya and H. Qin, *Tetrahedron*, 2000, **56**, 917 and references cited therein.
2 S. G. Davies, G. J.-M. Doisneau, J. C. Prodger and H. J. Sanganee, *Tetrahedron Lett.*, 1994, **35.**
3 S. G. Davies and D. J. Dixon, *Synlett*, 1998, 963.
4 D. J. Dixon and S. G. Davies, *Chem. Commun.*, 1996, 1797.
5 S. G. Davies, G. J.-M. Doisneau, J. C. Prodger and H. J. Sanganee, *Tetrahedron Lett.*, 1994, **35**, 2373.
6 C. Brown, *Chirality in Drug Design and Synthesis*, Academic Press, London, 1990.
7 Y. Nagao, W.-M. Dai, M. Ochiai and M. Shiro, *J. Org. Chem.*, 1989, **54**, 5211.
8 Y. Nagao, T. Ikeda, T. Inoue, M. Yagi, M. Shiro and E. Fujita, *J. Org. Chem.*, 1985, **50**, 4072.
9 Y. Nagao, T. Kumagai, S. Yamada, E. Fujita, Y. Inoue, Y. Nagase, S. Aoyagi and T. Abe, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2361.
10 J. Kenyon, H. Phillips and V. P. Pittman, *J. Chem. Soc.*, 1935, 1072.
11 D. Parker, *Chem. Rev.*, 1991, **91**, 1441.
12 For a review see E. S. Wallis and J. F. Lane, *Org. React.*, 1946, **3**, 267.
13 For a related study in which enantiopure succinic acids are converted to the respective β-amino acids *via* sequential auxiliary hydrolysis and Curtius rearrangement see D. A. Evans, L. D. Wu, J. J. M. Wiener, J. S. Johnson, D. H. B. Ripin and J. S. Tedrow, *J. Org. Chem.*, 1999, **64**, 6411.
14 A. S. Radhakrishna, M. E. Parham, R. M. Riggs and G. M. Loudon, *J. Org. Chem.*, 1979, **44**, 1747.
15 W. Leithe, *Chem. Ber.*, 1932, **65**, 660.
16 M. D. Rozwadowska, *Tetrahedron: Asymmetry*, 1993, **7**, 1619.
17 See footnote 5 of D. A. Evans and S. L. Bender, *Tetrahedron Lett.*, 1986, **7**, 799.
18 D. C. Braddock, D. Phil. Thesis, Oxford, 1995.
19 M.-C. Fournie-Zaluski, A. Coulard, R. Bouboutou, P. Chaillet, J. Devin, G. Waksman, J. Costentin and B. P. Roques, *J. Med. Chem.*, 1985, **28**, 1158.
20 I. S. Blagbrough, P. A. Coates, D. J. Hardick, T. Lewis, M. G. Rowan, S. Wonnacott and B. V. L. Potter, *Tetrahedron Lett.*, 1994, **35**, 8705.
21 A. Fredenhagen, S. Y. Tamura, P. T. M. Kenny, H. Komura, Y. Naya and K. Nakanishi, *J. Am. Chem. Soc.*, 1987, **109**, 4409.
22 S. Puertas, F. Robolledo and V. Gotor, *Tetrahedron*, 1995, **51**, 1495.
23 S. G. Davies, D. J. Dixon, G. J.-M. Doisneau, J. C. Prodger and H. J. Sanganee, *Tetrahedron: Asymmetry*, 2002, **13**, 647.