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Asymmetric synthesis and applications of β-amino Weinreb amides: asymmetric synthesis of (*S*)-coniine

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Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to a range of α,β-unsaturated Weinreb amides proceeds with high levels of diastereoselectivity (>95% de). The β-amino Weinreb amide products may be transformed into β-amino ketones *via* reactions with Grignard reagents, while treatment with DIBAL-H furnishes β-amino aldehydes. Trapping of the aldehyde *via* Wadsworth–Emmons reaction and subsequent manipulation offers an efficient route to homochiral δ-amino acid derivatives and 2-substituted piperidines. The application of this methodology for the synthesis of (*S*)-coniine is demonstrated.

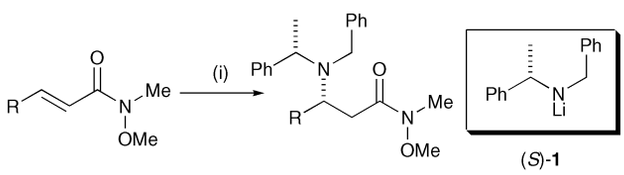
Introduction

N-protected α-amino aldehydes and ketones have been widely used as building blocks in natural product synthesis,[1] and are attractive chiral synthons for the preparation of amino sugars,[2] amino acids[3] and pyrrolidines.[4] In contrast, their β-amino analogues have received much less attention, with relatively few reports of the asymmetric synthesis of homochiral β-amino aldehydes and ketones. Approaches toward these synthetic targets include the oxidation of γ-amino alcohols[5] and the selective reduction of *N*-protected-β-amino esters,[6,7] although their inherent instability[8] has precluded a general method for their synthesis.[9] Previous investigations from this laboratory have shown that the highly diastereoselective conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to a range of α,β-unsaturated esters and subsequent *N*-deprotection offers an efficient route to the asymmetric synthesis of β-amino acids and derivatives.[10] In order to apply this methodology to the asymmetric synthesis of β-amino aldehydes and ketones, we investigated whether β-amino Weinreb amides[11] would provide β-amino aldehydes and ketones *via* reaction with hydride and organometallic reagents. We report herein our investigations within this area, utilising the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (*S*)-**1** to a range of α,β-unsaturated Weinreb amides and subsequent transformations. Part of this work has been communicated previously.[12]

Results and discussion

Preparation of β-amino aldehydes and ketones

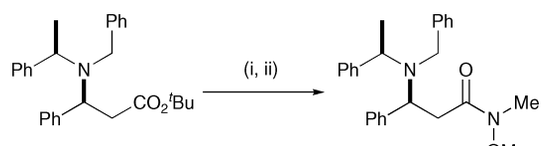
Initial studies concentrated upon the susceptibility of α,β-unsaturated *N*-methoxy-*N*-methylamides toward conjugate additions of lithium (*S*)-*N*-α-methylbenzyl-*N*-benzylamide **1**. The suitability of this lithium amide methodology for conjugate addition to α,β-unsaturated *N*-methoxy-*N*-methylamides is not immediately apparent, as Weinreb amides have been shown to decompose upon exposure to highly basic reagents, presumably due to the instability of their enolates.[13] Furthermore, only limited examples of enolate formation from Weinreb amides have been demonstrated,[14] as they are known to be unstable with respect to a retro-ene process to eliminate formaldehyde.[15] However conjugate addition of (*S*)-**1** to α,β-unsaturated Weinreb amides **2**–**4** furnished β-amino Weinreb amides **5**–**7** in >95% de and in uniformly excellent (>90%) isolated yield. The nature of these reactions suggests that the enolates of Weinreb amides prepared in this way are completely stable under the reaction conditions (Scheme 1).



2, R = Ph — **5**, R = Ph, 92%, >95% d.e.
3, R = Me — **6**, R = Me, 96%, >95% d.e.
4, R = ^{i}Pr — **7**, R = ^{i}Pr, 95%, >95% d.e.

Scheme 1 *Reagents and conditions*: (i) (*S*)-**1**, THF, −78 °C then NH_4Cl(aq).

The absolute configuration of the C(3) stereogenic centre of β-amino Weinreb amides **5**–**7** was assigned in each case by analogy with the model previously developed to explain the stereoselectivity observed during addition of lithium amide (*S*)-**1** to α,β-unsaturated acceptors.[16] This assignment was confirmed by the synthesis of an authentic sample of *ent*-**5** from the known β-amino ester **8**, the absolute configuration of which has previously been confirmed by its conversion to β-phenylalanine (Scheme 2).[17]



8 **5**

Scheme 2 *Reagents and conditions*: (i) TFA, DCM (1 : 1), rt; (ii) (MeO)MeNH·HCl, DCC/DMAP, NEt_3, rt.

With the range of β-amino *N*-methoxy-*N*-methyl amides **5**–**7** in hand, their conversion to β-amino ketones was investigated. Thus, treatment of β-amino amide (3*R*,α*S*)-**5** with PhMgBr utilising the reaction conditions previously developed by Weinreb and Nahm[11] gave the expected β-amino ketone (3*R*,α*S*)-**9** in 84% yield. Similar treatment of the β-amino amides (3*S*,α*S*)-**6** and (3*R*,α*S*)-**7** with MeMgBr enabled the preparation of β-amino ketones (4*S*,α*S*)-**10** and (4*R*,α*S*)-**11** respectively in good yields (Scheme 3).

Attention next focused on the possibility of direct reduction of β-amino amides **5**–**7** to the corresponding β-amino alde-

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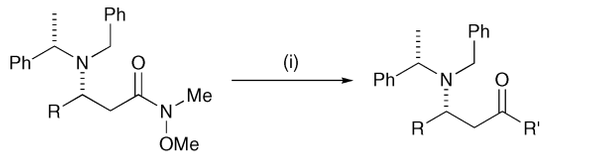
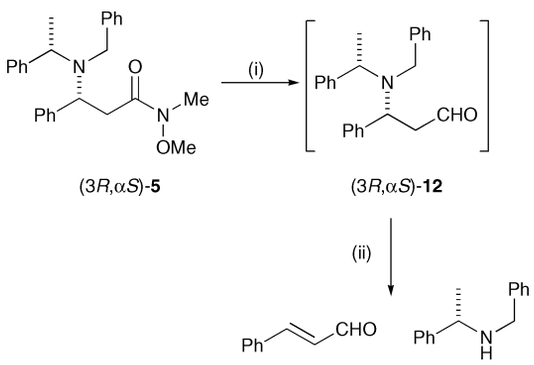


5, R = Ph
6, R = Me
7, R = ^{i}Pr

9, R = Ph, R' = Ph, 84%
10, R = Me, R' = Me, 88%
11, R = ^{i}Pr, R' = Me, 56%

Scheme 3 *Reagents and conditions*: (i) R'MgBr (3eq.), THF, 0 °C to rt.

hydes, which could then be used as key intermediates for the synthesis of δ-amino acid derivatives or 2-substituted piperidines after synthetic manipulation. In a model study, the treatment of 3-phenyl β-amino amide (3*R*,α*S*)-**5** with DIBAL-H in THF at −78 °C and subsequent protic work-up showed, by ^{1}H NMR spectroscopic analysis, that the reaction had proceeded to good conversion, furnishing the *N*,*N*-protected β-amino aldehyde **12**.[18] Attempts to obtain analytically pure β-amino aldehyde **12** *via* chromatographic purification on silica led to amine elimination, consistent with the well documented instability of β-amino aldehydes (Scheme 4).[8]

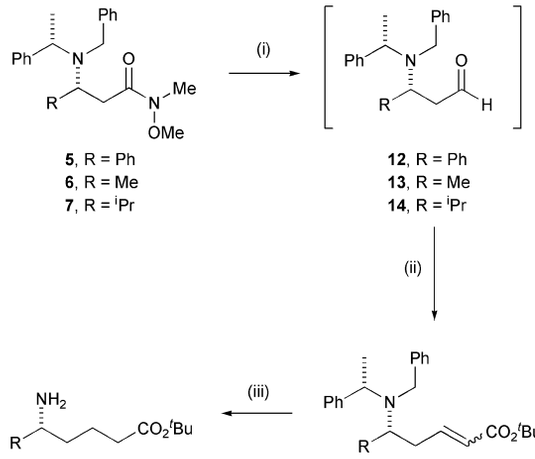


(3*R*,α*S*)-**5**

(3*R*,α*S*)-**12**

Scheme 4 *Reagents and conditions*: (i) DIBAL-H, THF, −78 °C; (ii) SiO_2 chromatography.

The possibility of trapping the intermediate aldehyde **12** *in situ* with a Wadsworth–Emmons reagent to generate the corresponding α,β-unsaturated ester was next considered. Attempts at a tandem "one-pot" DIBAL-H/Wadsworth–Emmons approach resulted in only the formation of the aldehyde by ^{1}H NMR spectroscopic analysis, indicating that the aluminium complex formed during reduction was stable under the reaction conditions, presumably only furnishing aldehyde **12** upon protic work-up. Investigations therefore focused on a stepwise approach to this transformation, forming first the β-amino aldehydes **12**–**14**[19] by reduction of β-amino amides **5**–**7** with DIBAL-H, followed by protic work-up and subsequent Wadsworth–Emmons reaction. Application of this protocol to β-amino Weinreb amide **5** gave excellent conversion to the required *N*,*N*-protected *tert*-butyl δ-amino α,β-unsaturated esters (*E*)-**15** : (*Z*)-**16** in an 89 : 11 ratio.[20] Purification allowed isolation of the separable diastereoisomeric products (*E*)-**15** and (*Z*)-**16** in 83% and 2% yield respectively (85% overall). Similar treatment of β-amino Weinreb amides **6** and **7** gave the *tert*-butyl δ-amino α,β-unsaturated esters (*E*)-**17** : (*Z*)-**18** and (*E*)-**19** : (*Z*)-**20** respectively with high diasteroselectivity, furnishing the separable (*E*)- and (*Z*)-diastereoisomers in high yields after chromatography. Subsequent hydrogenolysis and hydrogenation of (*E*)-**15**, (*E*)-**17** and (*E*)-**19** gave the δ-amino acid *tert*-butyl esters **21**–**23** in 94–98% yield and >95% ee respectively, as determined by chemical derivatisation with both homochiral and racemic Mosher's acid chlorides and ^{1}H and ^{19}F NMR spectroscopic analysis of the resulting amides (Scheme 5).



5, R = Ph
6, R = Me
7, R = ^{i}Pr

12, R = Ph
13, R = Me
14, R = ^{i}Pr

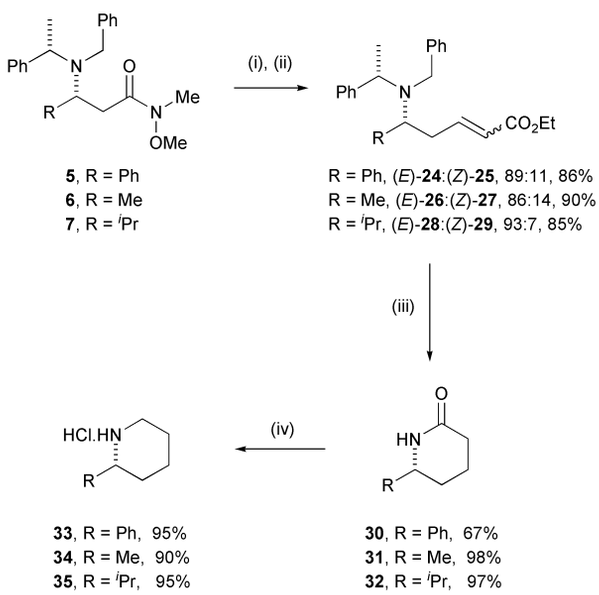
21, R = Ph, 94%, 96% e.e.
22, R = Me, 98%, 95% e.e.
23, R = ^{i}Pr, 97%, 98% e.e.

R = Ph, (*E*)-**15**:(*Z*)-**16**, 89:11, 85%
R = Me, (*E*)-**17**:(*Z*)-**18**, 90:10, 84%
R = ^{i}Pr, (*E*)-**19**:(*Z*)-**20**, 93:7, 87%

Scheme 5 *Reagents and conditions*: (i) DIBAL-H, hexanes, THF, 0 °C then acetone, sat. $C_4H_4KNaO_{6(aq).}$(Rochelle salt); (ii) $(EtO)_2POCH_2CO_2{}^{t}Bu$, *n*-BuLi, THF, −78 °C to rt; (iii) H_2 (5atm), $Pd(OH)_2$ on C, MeOH.

Application to the asymmetric synthesis of piperidines

The combination of this conjugate addition and DIBAL-H/Wadsworth–Emmons methodology was extended further for the asymmetric synthesis of homochiral δ-lactams and 2-alkylpiperidines.[21] Treatment of β-amino amides **5**–**7** with DIBAL-H and reaction of the crude reaction mixture with the lithium anion of triethylphosphonoacetate gave the separable ethyl δ-amino α,β-unsaturated esters (*E*)-**24** : (*Z*)-**25**, (*E*)-**26** : (*Z*)-**27** and (*E*)-**28** : (*Z*)-**29** respectively in high yields (85–90%) and with high diastereoselectivity. Concurrent hydrogenation and hydrogenolysis of (*E*)-**24**, (*E*)-**26** and (*E*)-**28**, and treatment of the resulting mixture in toluene at reflux gave δ-lactams **30**–**32** in high yields. Reduction of δ-lactams **30**–**32** with $LiAlH_4$ gave, after treatment with HCl in Et_2O and purification, (*R*)-2-phenylpiperidine hydrochloride **33** {$[a]_D^{23}$ −2.8 (*c* = 1.0, MeOH), lit.[22] $[a]_D^{23}$ −3.1 (*c* = 1.0, MeOH)}, (*S*)-2-methylpiperidine hydrochloride {(*S*)-pipecoline hydrochloride} **34** {$[a]_D^{23}$ −3.6 (*c* = 1.1, EtOH); lit.[23] *ent* $[a]_D^{23}$ +4.0 (*c* = 2, EtOH)} and (*R*)-2-*iso*-propylpiperidine hydrochloride **35** (Scheme 6).



5, R = Ph
6, R = Me
7, R = ^{i}Pr

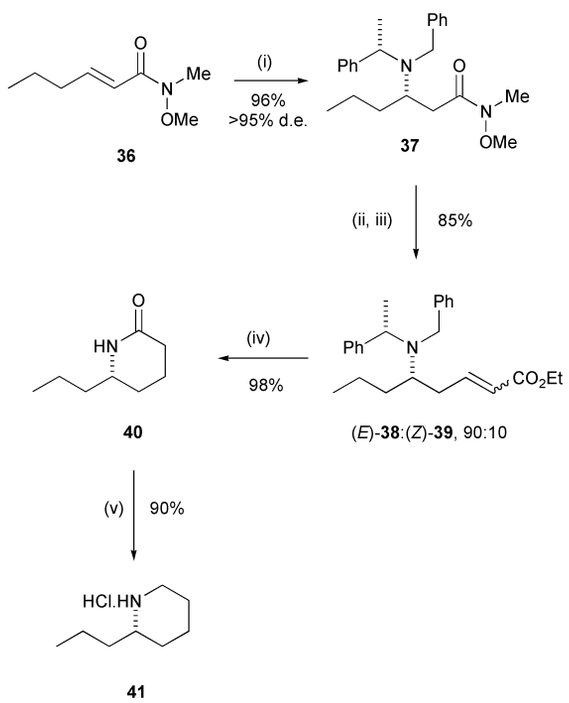
R = Ph, (*E*)-**24**:(*Z*)-**25**, 89:11, 86%
R = Me, (*E*)-**26**:(*Z*)-**27**, 86:14, 90%
R = ^{i}Pr, (*E*)-**28**:(*Z*)-**29**, 93:7, 85%

33, R = Ph, 95%
34, R = Me, 90%
35, R = ^{i}Pr, 95%

30, R = Ph, 67%
31, R = Me, 98%
32, R = ^{i}Pr, 97%

Scheme 6 *Reagents and conditions*: (i) DIBAL-H, hexanes, THF, 0 °C then acetone, sat. $C_4H_4KNaO_{6(aq).}$ (Rochelle salt); (ii) $(EtO)_2POCH_2CO_2Et$, *n*-BuLi, THF, −78 °C to rt; (iii) H_2 5 atm, $Pd(OH)_2$ on C, MeOH; then PhMe, Δ; (iv) $LiAlH_4$, Et_2O, Δ then HCl.

To demonstrate further the utility of this methodology in natural product synthesis, this procedure was applied to the asymmetric synthesis of (*S*)-2-propylpiperidine [(*S*)-coniine],[24] an alkaloid known to have potent neurotoxic effects.[25] Conjugate addition of (*S*)-**1** to (*E*)-*N*-methoxy-*N*-methyl hex-2-enamide **36** furnished (3*S*,α*S*)-*N*-methoxy-*N*-methyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-hexanamide **37** in 96% yield and in >95% de. Subsequent DIBAL-H/Wadsworth–Emmons reaction using triethylphosphonoacetate gave a separable 90 : 10 mixture of (*E*)-**38** and (*Z*)-**39** in 80% and 5% yield respectively (85% combined yield), with hydrogenation and hydrogenolysis, followed by heating in toluene to promote cyclisation, affording (*S*)-6-propylpiperidin-2-one[5] **40** in 98% yield. Reduction with $LiAlH_4$ gave, after treatment with HCl in Et_2O, (*S*)-coniine as its hydrochloride salt **41** with specific rotation {$[a]_D^{23}$ +9.1 (*c* = 0.6, EtOH), lit.[26] $[a]_D^{23}$ +9.4 (*c* = 0.3, EtOH)} and spectroscopic data in excellent agreement with the literature (Scheme 7).



Scheme 7 *Reagents and conditions*: (i) (*S*)-**1**, THF, −78 °C; (ii) DIBAL-H, hexanes, THF, 0 °C then acetone, sat. $C_4H_4KNaO_{6(aq)}$. (Rochelle salt); (iii) $(EtO)_2POCH_2CO_2Et$, *n*-BuLi, THF, −78 °C; (iv) H_2, $Pd(OH)_2$/C, MeOH then PhMe, Δ; (v) $LiAlH_4$, Et_2O, Δ then HCl, Et_2O.

Conclusions

In conclusion, conjugate addition of homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide to a range of α,β-unsaturated Weinreb amides proceeds efficiently with high diastereoselectivity to generate the β-amino Weinreb amides. Subsequent transformation to the corresponding β-amino ketone or β-amino aldehyde can be achieved readily by treatment with suitable organometallic reagents. Trapping of the β-amino aldehyde with a lithiated phosphonate furnishes α,β-unsaturated-δ-amino esters, which are viable precursors for δ-amino acid derivatives and 2-substituted piperidines. The further application of this methodology for the synthesis of polyamino natural products and polysubstituted homochiral piperidines is currently under investigation in our laboratory.

Experimental

General

All reactions involving organometallic or other moisture sensitive reagents were performed under an atmosphere of dry nitrogen *via* standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. THF and Et_2O were distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. Water was distilled. *n*-BuLi was used as a 2.5 M solution in hexanes (Aldrich). PhMgBr and MeMgBr were used as 3.0 M solutions in Et_2O (Aldrich). DIBAL-H was used as a 1.0 M solution in hexanes (Aldrich). $LiAlH_4$ was used as a 1.0 M solution in THF (Aldrich). All other solvents and reagents were used as supplied (Analytical or HPLC grade), without prior purification. All reactions were dried with $MgSO_4$. Thin layer chromatography was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Column chromatography was performed on Kieselgel 60 silica. Nuclear magnetic resonance spectra were recorded on either a Bruker DPX 400 spectrometer (^{1}H: 400 MHz and ^{13}C: 100 MHz) or a Bruker DPX 200 spectrometer (^{1}H: 200 MHz and ^{13}C: 50 MHz) in the deuterated solvent stated. Residual signals from the solvents were used as an internal reference. All chemical shifts (δ) are quoted in ppm and coupling constants (*J*) in Hz. In all cases the reaction diastereoselectivity was assessed by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture. Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using either a thin film on NaCl plates (film) or a KBr disc (KBr) as stated. Only the characteristic peaks are quoted in cm^{-1}. Low-resolution mass spectra (*m*/*z*) were recorded on either a VG MassLab 20–250 spectrometer or a Micromass Platform 1 spectrometer. High-resolution mass spectra (HRMS) were recorded on either a Micromass Autospec 500 OAT spectrometer or a Waters 2790 Micromass LCT electrospray ionisation mass spectrometer. Techniques used were chemical ionisation (CI), atmospheric pressure chemical ionisation (APCI) and electrospray ionisation (ESI) using partial purification by HPLC with methanol : acetonitrile : water (40 : 40 : 20) as eluent. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell and specific rotations are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g per 100 mL. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of Inorganic Chemistry Laboratory, Oxford.

General procedure 1 for the preparation of β-amino Weinreb amides

n-BuLi was added dropwise *via* syringe to a stirred solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine in THF at −78 °C. After thirty minutes a solution of the α,β-unsaturated Weinreb amide in THF at −78 °C was added dropwise *via* cannula. After a further two hours the reaction mixture was quenched with saturated aqueous NH_4Cl solution and allowed to warm to rt. The organic phase was separated and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were dried, filtered, and concentrated *in vacuo*. The residue was suspended in 10% aqueous citric acid solution and extracted three times with DCM. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, dried, filtered, and concentrated *in vacuo*. The residue was then purified *via* column chromatography.

General procedure 2 for the preparation of β-amino ketones

The Grignard reagent was added dropwise *via* syringe to a stirred solution of the β-amino Weinreb amide in THF at −78 °C. The reaction mixture was allowed to warm to rt over twelve hours before being quenched with saturated aqueous NH_4Cl solution. The organic phase was separated and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were dried, filtered, and concentrated *in vacuo*. The residue was then purified *via* column chromatography.

General procedure 3 for the preparation of α,β-unsaturated-δ-amino esters

DIBAL-H was added dropwise *via* syringe to a stirred solution of the β-amino Weinreb amide in THF at 0 °C. After thirty minutes the reaction mixture was quenched with acetone and cannulated into stirred, degassed, saturated aqueous sodium potassium tartrate solution at 0 °C. After a further thirty minutes the organic phase was separated and the aqueous phase was extracted three times with DCM. The combined organic extracts were dried, filtered, and concentrated *in vacuo*. The residue was dissolved immediately in THF and cooled to −78 °C before a solution of the Wadsworth–Emmons reagent, prepared by addition of *n*-BuLi to a solution of the requisite phosphonate in THF at −78 °C and stirred for thirty minutes, was added dropwise *via* cannula. The reaction mixture was allowed to warm to rt over four hours before being quenched with saturated aqueous NH_4Cl solution. The organic phase was separated and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were dried, filtered, and concentrated *in vacuo*. The residue was then purified *via* column chromatography.

General procedure 4 for the preparation of δ-amino esters

$Pd(OH)_2$/C was added to a vigorously stirred solution of the requisite *tert*-butyl α,β-unsaturated-δ-amino ester in degassed MeOH at rt and placed under a hydrogen atmosphere (5 atm). After twenty-four hours the reaction mixture was filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*.

General procedure 5 for the preparation of piperidin-2-ones

$Pd(OH)_2$/C was added to a vigorously stirred solution of the requisite ethyl α,β-unsaturated-δ-amino ester in degassed MeOH at rt and placed under a hydrogen atmosphere (5 atm). After twenty-four hours the reaction mixture was filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was dissolved in toluene and refluxed for twelve hours before being concentrated *in vacuo*. The residue was then purified *via* column chromatography.

General procedure 6 for the preparation of piperidine hydrochlorides

$LiAlH_4$ was added dropwise *via* syringe to a stirred solution of the requisite piperidin-2-one in Et_2O at 0 °C. The reaction mixture was refluxed for twelve hours before being quenched with 2 M aqueous KOH solution. The organic phase was separated and the aqueous phase was extracted three times with Et_2O. The combined organic extracts were dried, filtered, and poured into saturated ethereal HCl solution at 0 °C before being concentrated *in vacuo*. The residue was then purified *via* column chromatography.

(3*R*,α*S*)-*N*-Methoxy-*N*-methyl 3-(*N*′-benzyl-*N*′-α-methylbenzylamino)-3-phenylpropanamide 5

Following *general procedure 1*, *n*-BuLi (19.5 mL, 48.7 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (10.5 mL, 50.3 mmol) in THF (50 mL), and α,β-unsaturated Weinreb amide **2** (6.00 g, 31.4 mmol) in THF (20 mL) gave, after purification *via* column chromatography (pentane : Et_2O 10 : 1), the title compound **5** as a colourless oil (11.6 g, 92%, >95% de); $C_{26}H_{30}N_2O_2$ requires C, 77.6; H, 7.5; N, 7.0%; found C, 77.4; H, 7.2; N, 7.4%; $[\alpha]_D^{22}$ −23.8 (*c* = 1.1, $CHCl_3$); ν_{max} (film) 1662 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* = 6.9, C(α)*Me*), 2.63 (1H, dd, *J* = 15.5, *J* = 4.5, C(2)H_A), 2.94–2.98 (1H, br m, C(2)H_B), 3.04 (3H, s, NCH_3), 3.36 (3H, s, OCH_3), 3.84 (2H, ABq, J_{AB}=15.5, N′CH_2), 4.11 (1H, q, *J* = 6.9, C(α)*H*), 4.70 (1H, dd, *J* = 9.8, *J* = 4.5, C(3)*H*), 7.23–7.56 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.6, 32.0, 35.1, 51.0, 56.8, 59.1, 61.0, 126.6, 126.8, 127.1, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 142.1, 142.8, 144.3, 172.5; *m*/*z* (APCI) 403 (MH^+, 100%), 299 (76), 105 (32); HRMS (ESI) $C_{26}H_{31}N_2O_2^+$ requires 403.2386; found 403.2384.

(3*S*,α*S*)-*N*-Methoxy-*N*-methyl 3-(*N*′-benzyl-*N*′-α-methylbenzylamino)butanamide 6

Following *general procedure 1*, *n*-BuLi (28.8 mL, 72.1 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (15.6 mL, 74.4 mmol) in THF (50 mL), and α,β-unsaturated Weinreb amide **3** (6.00 g, 46.5 mmol) in THF (20 mL) gave, after purification *via* column chromatography (pentane : Et_2O 10 : 1), the title compound **6** as a colourless oil (15.2 g, 96%, >95% de); $C_{21}H_{28}N_2O_2$ requires C, 74.1; H, 8.3; N, 8.2%; found C, 73.8; H, 8.5; N, 8.1%; $[\alpha]_D^{22}$ −29.1 (*c* = 1.1, $CHCl_3$); ν_{max} (film) 1657 (C=O); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* = 6.7, C(4)H_3), 1.40 (3H, d, *J* = 7.0, C(α)*Me*), 2.32–2.44 (2H, m, C(2)H_2), 3.09 (3H, s, NCH_3), 3.41 (3H, s, OCH_3), 3.52–3.59 (1H, m, C(3)*H*), 3.81 (2H, ABq, J_{AB}=14.8, N′CH_2), 3.95 (1H, q, *J* = 7.0, C(α)*H*), 7.21–7.51 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.4, 18.7, 32.0, 37.2, 49.3, 49.8, 58.0, 60.9, 126.5, 126.6, 127.8, 127.9, 128.0, 128.2, 142.2, 144.6, 173.2; *m*/*z* (APCI) 341 (MH^+, 100%), 237 (89), 105 (42); HRMS (ESI) $C_{21}H_{29}N_2O_2^+$ requires 341.2229; found 341.2216.

(3*R*,α*S*)-*N*-Methoxy-*N*-methyl 3-(*N*′-benzyl-*N*′-α-methylbenzylamino)-4-methylpentanamide 7

Following *general procedure 1*, *n*-BuLi (23.7 mL, 59.2 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (12.8 mL, 61.1 mmol) in THF (50 mL), and α,β-unsaturated Weinreb amide **4** (6.00 g, 38.2 mmol) in THF (20 mL) gave, after purification *via* column chromatography (pentane : Et_2O 10 : 1), the title compound **7** as a colourless oil (13.4 g, 95%, >95% de); $C_{23}H_{32}N_2O_2$ requires C, 75.0; H, 8.8; N, 7.6%; found C, 74.9; H, 9.1; N, 7.6%; $[\alpha]_D^{22}$ −37.4 (*c* = 1.0, $CHCl_3$); ν_{max} (film) 1667 (C=O); δ_H (400 MHz, $CDCl_3$) 0.93, 1.15 (2 × 3H, d, *J* = 6.7, CH(CH_3)$_2$), 1.47 (3H, d, *J* = 7.1, C(α)*Me*), 1.71–1.82 (2H, m, C*H*(CH$_3$)$_2$, C(2)H_A), 2.37–2.43 (1H, br m, C(2)H_B), 3.11 (3H, s, NCH_3), 3.44 (3H, s, OCH_3), 3.51–3.55 (1H, m, C(3)*H*), 3.59 (1H, d, *J* = 15.0, N′CH_A), 3.83 (1H, q, *J* = 7.1, C(α)*H*), 3.89 (1H, d, *J* = 15.0, N′CH_B), 7.23–7.56 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.8, 20.0, 20.8, 31.6, 32.4, 32.8, 51.4, 56.7, 57.6, 60.9, 126.6, 126.8, 127.9, 128.0, 128.2, 128.3, 141.6, 142.1, 173.9; *m*/*z* (APCI) 369 (MH^+, 100%) 265 (43), 105 (24); HRMS (ESI) $C_{23}H_{33}N_2O_2^+$ requires 369.2542; found 369.2542.

(3*R*,α*S*)-3-(*N*-Benzyl-*N*-α-methylbenzylamino)-1,3-diphenylpropan-1-one 9

Following *general procedure 2*, PhMgBr (0.3 mL, 0.90 mmol) and β-amino Weinreb amide **5** (180 mg, 0.45 mmol) in THF (10 mL) gave, after purification by column chromatography (pentane : Et_2O 4 : 1), the title compound **9** as a colourless oil (158 mg, 84%); $C_{30}H_{29}NO$ requires C, 85.9; H, 7.0; N, 3.3%; found C, 86.2; H, 6.8; N, 3.6%; $[\alpha]_D^{22}$ −2.0 (*c* = 0.9, $CHCl_3$); ν_{max} (film) 1684 (C=O); δ_H (200 MHz, $CDCl_3$) 1.34 (3H, d, *J* = 6.9, C(α)*Me*), 3.09 (1H, dd, *J* = 16.7, *J* = 4.6, C(2)H_A), 3.35 (1H, dd, *J* = 16.7, *J* = 9.1, C(2)H_B), 3.78 (2H, ABq, J_{AB}=14.7, NCH_2), 4.05 (1H, q, *J* = 6.9, C(α)*H*), 4.78 (1H, dd, *J* = 9.1, *J* = 4.6, C(3)*H*), 7.16–7.66 (20H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 15.9, 41.4, 50.9, 56.7, 58.3, 126.6, 126.8, 127.0, 127.2, 127.9, 128.1, 128.2, 128.4, 128.8, 129.0, 132.8, 136.9, 141.2, 141.6, 142.4, 143.9, 198.4; *m*/*z* (CI) 420 (MH^+, 22%), 212 (100), 209 (79), 105 (30).

(4*S*,α*S*)-4-(*N*-Benzyl-*N*-α-methylbenzylamino)pentan-2-one 10

Following *general procedure 2*, MeMgBr (0.4 mL, 1.06 mmol) and β-amino Weinreb amide **6** (180 mg, 0.53 mmol) in THF (10 mL) gave, after purification *via* column chromatography (pentane : Et_2O 4 : 1), the title compound **10** as a colourless oil

(138 mg, 88%); $C_{20}H_{25}NO$ requires C, 81.3; H, 8.5; N, 4.7%; found C, 81.2; H, 8.7; N, 4.5%; $[\alpha]_D^{22}$ −20.0 (*c* = 1.0, $CHCl_3$); ν_{max} (film) 1684 (C=O); δ_H (200 MHz, $CDCl_3$) 1.14 (3H, d, *J* = 6.6, C(5)H_3), 1.37 (3H, d, *J* = 6.9, C(α)*Me*), 1.76 (3H, s, C(1)H_3), 2.20 (1H, dd, *J* = 15.0, *J* = 8.0, C(3)H_A), 2.42 (1H, dd, *J* = 15.0, *J* = 5.4, C(3)H_B), 3.42–3.59 (1H, m, C(4)*H*), 3.72 (2H, ABq, J_{AB}=14.8, NCH_2), 3.88 (1H, q, *J* = 6.9, C(α)*H*), 7.18–7.46 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 17.6, 18.9, 29.6, 48.5, 49.0, 49.6, 57.5, 126.7, 126.8, 127.8, 128.1, 128.2, 128.4, 141.6, 143.9, 208.3; *m*/*z* (CI) 296 (MH^+, 13%), 212 (100), 105 (10), 85 (11).

(4*R*,α*S*)-4-(*N*-Benzyl-*N*-α-methylbenzylamino)-5-methylhexan-2-one 11

Following *general procedure 2*, MeMgBr (0.3 mL, 0.98 mmol) and β-amino Weinreb amide **7** (180 mg, 0.49 mmol) in THF (10 mL) gave, after purification *via* column chromatography (pentane : Et_2O 4 : 1), the title compound **11** as a colourless oil (89 mg, 56%); $C_{22}H_{29}NO$ requires C, 81.7; H, 9.0; N, 4.3%; found C, 81.6; H, 8.8; N, 4.6%; $[\alpha]_D^{22}$ −27.1 (*c* = 2.0, $CHCl_3$); ν_{max} (film) 2963 (C–H), 1717 (C=O); δ_H (200 MHz, $CDCl_3$) 0.81, 1.13 (2 × 3H, d, *J* = 6.7, CH(CH_3)$_2$), 1.42 (3H, d, *J* = 7.1, C(α)*Me*), 1.61–1.68 (1H, m, C*H*(CH$_3$)$_2$), 1.85 (3H, s, C(1)H_3), 2.17–2.25 (2H, m, C(3)H_2), 3.37–3.41 (1H, m, C(4)*H*), 3.53 (1H, d, *J* = 14.9, NCH_A), 3.76 (1H, d, *J* = 14.9, NCH_B), 3.77 (1H, q, *J* = 7.1, C(α)*H*), 7.22–7.50 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 19.6, 19.7, 20.8, 29.8, 32.5, 44.0, 51.3, 55.7, 57.2, 126.6, 126.9, 127.9, 128.0, 128.2, 128.3, 141.3, 141.5, 207.2; *m*/*z* (CI) 324 (MH^+, 12%), 212 (100), 112 (14), 105 (23).

(2*Z*,5*R*,α*S*)- and (2*E*,5*R*,α*S*)-*tert*-butyl 5-(*N*-benzyl-*N*-α-methylbenzylamino)-5-phenylpent-2-enoate (*Z*)-16 and (*E*)-15

Following *general procedure 3*, DIBAL-H (24.9 mL, 24.9 mmol), β-amino Weinreb amide **5** (5.00 g, 12.4 mmol) in THF (20 mL), *n*-BuLi (6.0 mL, 14.9 mmol) and *tert*-butyl diethylphosphonoacetate (3.5 mL, 14.9 mmol) in THF (10 mL) gave, after purification and separation *via* column chromatography (pentane : Et_2O 80 : 1), (*Z*)-**16** (0.11 g, 2%) as a colourless oil; $[\alpha]_D^{23}$ −8.8 (*c* = 0.5, $CHCl_3$); ν_{max} (film) 1711 (C=O), 1638 (C=C); δ_H (400 MHz, $CDCl_3$) 1.06 (3H, d, *J* = 6.9, C(α)*Me*), 1.48 (9H, s, C(CH_3)$_3$), 3.00–3.08 (1H, m, C(4)H_A), 3.29–3.37 (1H, m, C(4)H_B), 3.80 (2H, ABq, J_{AB}=14.5, NCH_2), 3.90 (1H, dd, *J* = 8.5, *J* = 7.1, C(5)*H*), 4.16 (1H, q, *J* = 6.9, C(α)*H*), 5.62 (1H, d, *J* = 11.6, C(2)*H*), 5.85 (1H, app dt, *J* = 11.6, *J* = 7.0, C(3)*H*), 7.18–7.48 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.1, 28.1, 29.7, 50.4, 56.5, 61.8, 80.0, 121.9, 125.5, 126.5, 126.6, 127.0, 127.8, 128.1, 128.3, 128.4, 128.6, 141.7, 141.8, 145.0, 147.0, 166.0; *m*/*z* (APCI) 442 (MH^+, 54%), 338 (12), 105 (100); HRMS (ESI) $C_{30}H_{36}NO_2^+$ requires 442.2746; found 442.2754; further elution gave (*E*)-**15** (4.57 g, 83%) as a colourless oil; $[\alpha]_D^{23}$ −20.3 (*c* = 1.0, $CHCl_3$); ν_{max} (film) 1712 (C=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* = 6.9, C(α)*Me*), 1.53 (9H, s, C(CH_3)$_3$), 2.49–2.57 (1H, m, C(4)H_A), 2.69–2.77 (1H, m, C(4)H_B), 3.78 (1H, d, *J* = 14.5, NCH_A), 3.90 (1H, d, *J* = 14.5, NCH_B), 4.01 (1H, dd, *J* = 8.7, *J* = 6.3, C(5)*H*), 4.15 (1H, q, *J* = 6.9, C(α)*H*), 5.65 (1H, d, *J* = 15.5, C(2)*H*), 6.72 (1H, app dt, *J* = 15.5, *J* = 7.1, C(3)*H*), 7.24–7.53 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.6, 28.2, 34.7, 50.6, 56.3, 61.6, 79.9, 124.3, 126.7, 126.8, 127.2, 127.7, 127.8, 128.2, 128.3, 128.4, 128.8, 141.4, 141.7, 144.5, 145.9, 165.8; *m*/*z* (APCI) 442 (MH^+, 12%), 338 (10), 105 (100); HRMS (ESI) $C_{30}H_{36}NO_2^+$ requires 442.2746; found 442.2735.

NMR data for intermediate (3*R*,α*S*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-5-phenylpropanal **12**: δ_H (200 MHz, $CDCl_3$) 1.14 (3H, d, *J* = 6.9, C(α)*Me*), 2.61 (1H, ddd, *J* = 16.2, *J* = 7.5, *J* = 1.8, C(2)H_A), 2.85 (1H, ddd, *J* = 16.2, *J* = 7.7, *J* = 3.0, C(2)H_B), 3.66 (1H, d, *J* = 14.0, NCH_A), 3.83 (1H, d, *J* = 14.0, NCH_B), 4.06 (1H, q, *J* = 6.9, C(α)*H*), 4.49–4.57 (1H, m, C(3)*H*), 7.22–7.61 (15H, m, *Ph*), 9.37 (1H, dd, *J* = 3.0. *J* = 1.8, C*H*O); δ_C (50 MHz, $CDCl_3$) 18.9, 25.6, 53.5, 57.4, 67.9, 126.7, 126.9, 127.0, 127.6, 127.8, 128.0, 128.3, 128.5, 128.6, 140.5, 142.3, 145.4, 193.8.

(2*Z*,5*S*,α*S*)- and (2*E*,5*S*,α*S*)-*tert*-butyl 5-(*N*-benzyl-*N*-α-methylbenzylamino)-hex-2-enoate (*Z*)-18 and (*E*)-17

Following *general procedure 3*, DIBAL-H (29.4 mL, 29.4 mmol), β-amino Weinreb amide **6** (5.00 g, 14.7 mmol) in THF (20 mL), *n*-BuLi (7.1 mL, 17.6 mmol) and *tert*-butyl diethylphosphonoacetate (4.1 mL, 17.6 mmol) in THF (10 mL) gave, after purification and separation *via* column chromatography (pentane : Et_2O 80 : 1), gave (*Z*)-**18** (0.11 g, 2%) as a colourless oil; $[\alpha]_D^{25}$ −86.7 (*c* = 0.6, $CHCl_3$), ν_{max} (film) 1712 (C=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* = 6.6, C(6)H_3), 1.35 (3H, d, *J* = 6.9, C(α)*Me*), 1.45 (9H, s, C(CH_3)$_3$), 2.51–2.59 (1H, m, C(4)H_A), 2.78–2.86 (1H, m, C(4)H_B), 2.91–2.96 (1H, m, C(5)*H*), 3.75 (2H, ABq, J_{AB}=14.2, NCH_2), 3.97 (1H, q, *J* = 6.9, C(α)*H*), 5.59 (1H, d, *J* = 11.4, C(2)*H*), 5.83 (1H, app dt, *J* = 11.4, *J* = 6.6, C(3)*H*), 7.18–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5, 18.1, 28.2, 33.7, 49.4, 52.1, 56.7, 79.8, 121.3, 126.5, 126.6, 127.8, 127.9, 128.1, 128.5, 142.0, 144.9, 148.2, 172.3; *m*/*z* (APCI$^+$) 380 (MH^+, 38%), 276 (47), 105 (100); HRMS (ESI) $C_{25}H_{34}NO_2^+$ requires 380.2590; found 380.2592; further elution gave (*E*)-**17** (4.59 g, 82%) as a colourless oil; $[\alpha]_D^{23}$ −31.4 (*c* = 1.0, $CHCl_3$); ν_{max} (film) 1711 (C=O), 1649 (C=C); δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* = 6.6, C(6)H_3), 1.38 (3H, d, *J* = 6.9, C(α)*Me*), 1.54 (9H, s, C(CH_3)$_3$), 2.00–2.20 (1H, m, C(4)H_A), 2.28–2.35 (1H, m, C(4)H_B), 3.01–3.06 (1H, m, C(5)*H*), 3.79 (2H, ABq, J_{AB}=14.6, NCH_2), 3.98 (1H, q, *J* = 6.9, C(α)*H*), 5.65 (1H, d, *J* = 15.5, C(2)*H*), 6.71 (1H, app dt, *J* = 15.5, *J* = 7.8, C(3)*H*), 7.24–7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.6, 18.3, 28.2, 37.3, 49.6, 51.8, 57.3, 79.9, 123.9, 126.5, 126.6, 127.8, 128.0, 128.2, 128.3, 141.9, 144.6, 146.7, 165.9; *m*/*z* (APCI) 380 (MH^+, 32%), 276 (26), 105 (100); HRMS (ESI) $C_{25}H_{34}NO_2^+$ requires 380.2590; found 380.2601.

NMR data for intermediate (3*S*,α*S*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanal **13**: δ_H (200 MHz, $CDCl_3$) 1.13 (3H, d, *J* = 6.7, C(4)H_3), 1.40 (3H, d, *J* = 6.9, C(α)*Me*), 2.12 (1H, ddd, *J* = 16.4, *J* = 7.8, *J* = 2.0, C(2)H_A), 2.34–2.52 (1H, m, C(2)H_B), 3.49–3.66 (1H, m, C(3)*H*), 3.72 (2H, ABq, J_{AB}=14.5, NCH_2), 3.90 (1H, q, *J* = 6.9, C(α)*H*), 7.12–7.40 (10H, m, *Ph*), 9.08–9.13 (1H, m, C*H*O); δ_H (50 MHz, $CDCl_3$) 15.4, 18.3, 47.1, 48.9, 49.2, 56.4, 126.7, 126.9, 127.7, 127.9, 128.2, 128.5, 140.8, 143.8, 203.0.

(2*Z*,5*R*,α*S*)- and (2*E*,5*R*,α*S*)-*tert*-butyl 5-(*N*-benzyl-*N*-α-methylbenzylamino)-6-methylhept-2-enoate (*Z*)-20 and (*E*)-19

Following *general procedure 3*, DIBAL-H (27.2 mL, 27.2 mmol), β-amino Weinreb amide **7** (5.00 g, 13.6 mmol) in THF (20 mL), *n*-BuLi (6.5 mL, 16.3 mmol) and *tert*-butyl diethylphosphonoacetate (3.8 mL, 16.3 mmol) in THF (10 mL) gave, after purification and separation *via* column chromatography (pentane : Et_2O 80 : 1), (*Z*)-**20** (0.12 g, 2%) as a colourless oil; $[\alpha]_D^{25}$ −35.7 (*c* = 0.3, $CHCl_3$); ν_{max} (film) 1714 (C=O), 1636 (C=C); δ_H (400 MHz, $CDCl_3$) 0.92, 1.00 (2 × 3H, d, *J* = 6.8, CH(CH_3)$_2$), 1.32 (3H, d, *J* = 6.8, C(α)*Me*), 1.46 (9H, s, C(CH_3)$_3$), 1.79–1.83 (1H, m, C*H*(CH$_3$)$_2$), 2.26–2.30 (1H, m, C(4)H_A), 2.57–2.62 (1H, m, C(5)*H*), 2.80–2.84 (1H, m, C(4)H_B), 3.72 (1H, d, *J* = 15.2, NCH_A), 3.86 (1H, q, *J* = 6.8, C(α)*H*), 3.90 (1H, d, *J* = 15.2, NCH_B), 5.54 (1H, d, *J* = 11.5, C(2)*H*), 5.84 (1H, app dt, *J* = 11.5, *J* = 5.8, C(3)*H*), 7.21–7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.9, 20.3, 20.9, 28.1, 28.2, 31.9, 51.6, 58.4, 62.3, 79.7, 120.5, 126.3, 126.7, 127.8, 127.9, 128.0, 128.1, 142.1, 143.6, 149.4, 166.0; *m*/*z* (APCI) 408 (MH^+, 13%), 304 (21), 105 (100); HRMS (ESI) $C_{27}H_{38}NO_2^+$ requires 408.2903; found 408.2905; further elution gave (*E*)-**19** (4.68 g, 85%) as a colourless oils; $[\alpha]_D^{25}$ −5.1 (*c* = 1.5, $CHCl_3$), ν_{max} (film) 1713 (C=O), 1649 (C=C); δ_H (400 MHz, $CDCl_3$) 0.99, 1.01 (2 × 3H, d, *J* = 6.9, CH(CH_3)$_2$), 1.35 (3H, d, *J* = 6.9, C(α)*Me*), 1.52 (9H, s, C(CH_3)$_3$), 1.80–1.91 (2H, m, C(4)H_A, C*H*(CH$_3$)$_2$), 2.03–

2.11 (1H, m, C(4)H_B), 2.73–2.77 (1H, m, C(5)H), 3.69 (1H, d, J = 15.2, NCH_A), 3.85 (1H, q, J = 6.9, C(α)H), 3.90 (1H, d, J = 15.2, NCH_B), 5.53 (1H, d, J = 15.4, C(2)H), 6.70 (1H, app dt, J = 15.4. J = 6.6, C(3)H), 7.26–7.52 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.9, 20.4, 21.0, 28.2, 31.5, 32.0, 51.9, 58.2, 60.8, 80.0, 123.4, 126.6, 127.0, 128.0, 128.1, 128.2, 128.3, 141.7, 142.9, 147.8, 166.1; *m/z* (APCI) 408 (MH^+, 26%), 304 (37), 105 (100); HRMS (ESI) $C_{27}H_{38}NO_2^+$ requires 408.2903; found 408.2906.

NMR data for intermediate **(3*R*,α*S*)**-3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methylpentanal **14**: δ_H (200 MHz, $CDCl_3$) 0.85, 1.15 (2 × 3H, d, J = 6.7, CH(CH_3)$_2$), 1.43 (3H, d, J = 7.1, C(α)*Me*), 1.71–1.78 (1H, m, CH(CH$_3$)$_2$), 1.90–2.01 (1H, m, C(2)H_A), 2.22 (1H, ddd, J = 17.0, J = 8.0, J = 2.6, C(2)H_B), 3.25–3.35 (1H, m, C(3)H), 3.60 (1H, d, J = 14.7, NCH_A), 3.80 (1H, d, J = 14.7, NCH_B), 3.85 (1H, q, J = 7.1, C(α)H), 7.24–7.52 (10H, m, *Ph*), 9.40–9.41 (1H, m, CHO); δ_C (50 MHz, $CDCl_3$) 19.3, 20.1, 21.2, 32.1, 44.3, 51.2, 56.0, 57.2, 126.8, 127.2, 127.9, 128.0, 128.2, 128.4, 140.9, 141.6, 202.0.

(*R*)-*tert*-Butyl 5-amino-5-phenylpentanoate 21

Following *general procedure 4*, Pd(OH)$_2$/C (250 mg), *tert*-butyl α,β-unsaturated-δ-amino ester (*E*)-**15** (500 mg) in MeOH (5 mL), and H_2 (5 atm) gave the title compound **21** as a colourless amorphous solid (264 mg, 94%); mp 136–138 °C; $[\alpha]_D^{22}$ −25.5 (c = 0.5, $CHCl_3$); ν_{max} (KBr) 3410 (N-H), 1725 (C=O); δ_H (400 MHz, CD_3OD) 1.44 (9H, s, C(CH_3)$_3$), overlapping 1.38–1.54 (1H, m, C(3)H_A), 1.55–1.60 (1H, m, C(3)H_B), 1.99–2.07 (2H, m, C(4)H_2), 2.23–2.30 (2H, m, C(2)H_2), 4.28 (1H, dd, J = 9.1, J = 6.2, C(5)H), 7.45–7.52 (5H, m, *Ph*); δ_C (100 MHz, CD_3OD) 22.8, 28.7, 35.1, 35.9, 57.1, 82.1, 128.9, 130.8, 130.9, 138.4, 174.5; *m/z* (CI) 250 (MH^+, 100%), 194 (46); HRMS (CI) $C_{15}H_{24}NO_2^+$ requires 250.1807; found 250.1809.

(*S*)-*tert*-Butyl 5-aminohexanoate 22

Following *general procedure 4*, Pd(OH)$_2$/C (250 mg), *tert*-butyl α,β-unsaturated-δ-amino ester (*E*)-**17** (500 mg) in MeOH (5 mL), and H_2 (5 atm) gave the title compound **22** as a colourless amorphous solid (241 mg, 98%); mp 98–100 °C; $[\alpha]_D^{24}$ −1.5 (c = 0.9, $CHCl_3$); ν_{max} (KBr) 3410 (N-H), 1729 (C=O); δ_H (400 MHz, CD_3OD) 1.12 (3H, d, J = 6.6, C(6)H_3), 1.47 (9H, s, C(CH_3)$_3$) overlapping 1.34–1.48 (2H, m, C(4)H_2), 1.59–1.67 (2H, m, C(3)H_2), 2.26 (2H, app t, J = 7.2, C(2)H_2), 2.89–2.97 (1H, m, C(5)H); δ_C (100 MHz, CD_3OD) 22.8, 23.2, 28.8, 36.7, 39.5, 48.1, 81.9, 175.2; *m/z* (CI) 188 (MH^+, 100%), 132 (32); HRMS (CI) $C_{10}H_{22}NO_2^+$ requires 188.1651; found 188.1655.

(*R*)-*tert*-Butyl 5-amino-6-methylheptanoate 23

Following *general procedure 4*, Pd(OH)$_2$/C (250 mg), *tert*-butyl α,β-unsaturated-δ-amino ester (*E*)-**19** (500 mg) in MeOH (5 mL), and H_2 (5 atm) gave the title compound **23** as a colourless amorphous solid (255 mg, 97%); mp 92–94 °C; $[\alpha]_D^{24}$ +3.3 (c = 0.7, $CHCl_3$); ν_{max} (KBr) 3410 (N-H), 1727 (C=O); δ_H (400 MHz, CD_3OD) 1.02, 1.04 (2 × 3H, d, J = 6.9, CH(CH_3)$_2$), 1.47 (9H, s, C(CH_3)$_3$), 1.57–1.77 (4H, m, C(3)H_2, C(4)H_2), 1.93–2.05 (1H, m, CH(CH$_3$)$_2$), 2.32–2.35 (2H, m, C(2)H_2), 3.04–3.08 (1H, m, C(5)H); δ_C (100 MHz, CD_3OD) 17.1, 17.3, 20.9, 27.6, 29.1, 30.2, 34.7, 57.2, 80.7, 173.3; *m/z* (CI) 216 (MH^+, 100%), 160 (42); HRMS (CI) $C_{12}H_{26}NO_2^+$ requires 216.1964; found 216.1953.

(2*Z*,5*R*,α*S*)- and (2*E*,5*R*,α*S*)-ethyl 5-(*N*-benzyl-*N*-α-methylbenzylamino)-5-phenylpent-2-enoate (*Z*)-25 and (*E*)-24

Following *general procedure 3*, DIBAL-H (7.5 mL, 7.46 mmol), β-amino Weinreb amide **5** (1.50 g, 3.73 mmol) in THF (10 mL), *n*-BuLi (1.8 mL, 4.48 mmol) and triethylphosphonoacetate (0.9 mL, 4.48 mmol) in THF (5 mL) gave, after purification and separation *via* column chromatography (pentane : Et_2O 80 : 1), (*Z*)-**25** (0.08 g, 5%) as a colourless oil; $[\alpha]_D^{25}$ −8.0 (c = 1.0, $CHCl_3$); ν_{max} (film) 1715 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, J = 6.8, C(α)*Me*), 1.28 (3H, t, J = 7.1, OCH$_2$CH_3), 2.96–3.05 (1H, m, C(4)H_A), 3.31–3.39 (1H, m, C(4)H_B), 3.80 (2H, ABq, J_{AB}=14.5, NCH_2), 3.92 (1H, dd, J = 8.7, J = 6.8, C(5)H), 4.14 (1H, q, J = 6.8, C(α)H), 4.15 (2H, q, J = 7.1, OCH_2CH$_3$), 5.68 (1H, d, J = 11.5, C(2)H), 5.92 (1H, app dt, J = 11.5, J = 4.5, C(3)H), 7.17–7.47 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3, 15.7, 31.1, 50.4, 56.4, 59.8, 62.1, 120.1, 126.5, 127.1, 127.2, 127.8, 128.0, 128.1, 128.2, 128.5, 128.8, 141.7, 141.8, 144.9, 148.4, 166.4; *m/z* (APCI) 414 (MH^+, 14%), 310 (52), 105 (100); HRMS (ESI) $C_{28}H_{32}NO_2^+$ requires 414.2433; found 414.2428; further elution gave (*E*)-**24** (1.25 g, 81%) as a colourless oil; $[\alpha]_D^{25}$ −22.7 (c = 1.0, $CHCl_3$); ν_{max} (film) 1718 (C=O), 1653 (C=C); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, J = 6.8, C(α)*Me*), 1.27 (3H, t, J = 7.1, OCH$_2$CH_3), 2.49–2.57 (1H, m, C(4)H_A), 2.63–2.70 (1H, m, C(4)H_B), 3.78 (2H, ABq, J_{AB}=14.7, NCH_2), 3.97 (1H, dd, J = 9.1, J = 6.1, C(5)H), 4.09 (1H, q, J = 6.8, C(α)H), 4.14 (2H, q, J = 7.1, OCH_2CH$_3$), 5.65 (1H, d, J = 15.6, C(2)H), 6.72 (1H, app dt, J = 15.6, J = 7.2, C(3)H), 7.19–7.49 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2, 15.7, 34.7, 50.6, 56.3, 60.1, 61.6, 122.6, 126.6, 126.8, 127.2, 127.8, 128.1, 128.2, 128.3, 128.5, 128.6, 141.3, 141.4, 144.4, 147.0, 166.3; *m/z* (APCI) 414 (MH^+, 12%), 310 (47), 105 (100); HRMS (ESI) $C_{28}H_{32}NO_2^+$ requires 414.2433; found 414.2443.

(2*Z*,5*S*,α*S*)- and (2*E*,5*S*,α*S*)-ethyl 5-(*N*-benzyl-*N*-α-methylbenzylamino)hex-2-enoate (*Z*)-27 and (*E*)-26

Following *general procedure 3*, DIBAL-H (8.8 mL, 8.82 mmol), β-amino Weinreb amide **6** (1.50 g, 4.41 mmol) in THF (10 mL), *n*-BuLi (2.1 mL, 5.29 mmol) and triethylphosphonoacetate (1.1 mL, 5.29 mmol) in THF (5 mL) gave, after purification and separation *via* column chromatography (pentane : Et_2O 80 : 1), (*Z*)-**27** (0.14 g, 9%) as a colourless oil; $[\alpha]_D^{25}$ −90.7 (c = 0.9, $CHCl_3$); ν_{max} (film) 1716 (C=O), 1642 (C=C); δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, J = 6.7, C(6)H_3), 1.28 (3H, t, J = 7.2, OCH$_2$CH_3), 1.37 (3H, d, J = 6.9, C(α)*Me*), 2.59–2.67 (1H, m, C(4)H_A), 2.80–2.88 (1H, m, C(4)H_B), 2.95–3.01 (1H, m, C(5)H), 3.78 (2H, ABq, J_{AB}=14.4, NCH_2), 4.00 (1H, q, J = 6.9, C(α)H), 4.14 (2H, q, J = 7.2, OCH_2CH$_3$), 5.69 (1H, d, J = 11.6, C(2)H), 5.97 (1H, app dt, J = 11.6, J = 7.2, C(3)H), 7.20–7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3, 16.5, 18.1, 34.0, 49.4, 52.1, 56.8, 59.7, 119.5, 126.5, 126.6, 127.7, 127.9, 128.1, 128.5, 141.9, 144.9, 149.7, 166.6; *m/z* (APCI) 352 (MH^+, 28%), 248 (90), 105 (100); HRMS (ESI) $C_{23}H_{30}NO_2^+$ requires 352.2277; found 352.2285; further elution gave (*E*)-**26** (1.25 g, 81%) as a colourless oil; $[\alpha]_D^{25}$ −30.4 (c = 1.1, $CHCl_3$); ν_{max} (film) 1718 (C=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, J = 7.1, C(6)H_3), 1.34 (3H, t, J = 7.2, OCH$_2$CH_3), 1.38 (3H, d, J = 6.8, C(α)*Me*), 2.02–2.10 (1H, m, C(4)H_A), 2.29–2.36 (1H, m, C(4)H_B), 3.02–3.07 (1H, m, C(5)H), 3.80 (2H, ABq, J_{AB}=14.7, NCH_2), 3.98 (1H, q, J = 6.8, C(α)H), 4.23 (2H, q, J = 7.2, OCH_2CH$_3$), 5.72 (1H, d, J = 15.4, C(2)H), 6.78 (1H, app dt, J = 15.4, J = 7.8, C(3)H), 7.24–7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3, 17.4, 18.3, 37.5, 50.0, 51.8, 57.4, 60.1, 122.1, 126.6, 126.7, 127.6, 127.9, 128.0, 128.2, 141.8, 144.5, 148.0, 166.5; *m/z* (APCI) 352 (MH^+, 11%), 248 (88), 105 (100); HRMS (ESI) $C_{23}H_{30}NO_2^+$ requires 352.2277; found 352.2282.

(2*Z*,5*R*,α*S*)- and (2*E*,5*R*,α*S*)-ethyl 5-(*N*-benzyl-*N*-α-methylbenzylamino)-6-methylhept-2-enoate (*Z*)-29 and (*E*)-28

Following *general procedure 3*, DIBAL-H (8.2 mL, 8.15 mmol), β-amino Weinreb amide **7** (1.50 g, 4.08 mmol) in THF (10 mL), *n*-BuLi (2.0 mL, 4.89 mmol) and triethylphosphonoacetate (1.0 mL, 4.89 mmol) in THF (5 mL) gave, after purification and separation *via* column chromatography (pentane : Et_2O 80 : 1), (*Z*)-**29** (0.05 g, 3%) as a colourless oil; $[\alpha]_D^{25}$ −55.0 (c = 0.3, $CHCl_3$), ν_{max} (film) 1718 (C=O), 1654 (C=C); δ_H (400 MHz, $CDCl_3$) 0.91, 1.01 (2 × 3H, d, J = 6.7, CH(CH_3)$_2$), 1.27 (3H, t,

J = 7.1, OCH_2CH_3), 1.32 (3H, d, J = 7.0, C(α)*Me*), 1.75–1.87 (1H, m, $CH(CH_3)_2$), 2.23–2.31 (1H, m, C(4)H_A), 2.58–2.64 (1H, m, C(5)*H*), 2.82–2.91 (1H, m, C(4)H_B), 3.71 (1H, d, J = 15.4, NCH_A), 3.86 (1H, q, J = 7.0, C(α)*H*), 3.89 (1H, d, J = 15.4, NCH_B), 4.13 (2H, q, J = 7.1, OCH_2CH_3), 5.62 (1H, d, J = 11.5, C(2)*H*), 5.95 (1H, app dt, J = 11.5, J = 6.8, C(3)*H*), 7.20–7.53 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2, 19.9, 20.3, 20.9, 28.4, 31.9, 51.6, 58.3, 59.6, 62.2, 118.7, 126.3, 126.7, 127.8, 127.9, 128.0, 128.1, 142.0, 143.6, 150.9, 166.4; *m/z* (APCI) 380 (MH^+, 13%), 276 (86), 105 (100); HRMS (ESI) $C_{25}H_{34}NO_2^+$ requires 380.2590; found 380.2587; further elution gave (*E*)-**28** (1.27 g, 82%) as a colourless oil; $[\alpha]_D^{25}$ −9.1 (c = 1.4, $CHCl_3$); ν_{max} (film) 1718 (C=O), 1649 (C=C); δ_H (400 MHz, $CDCl_3$) 0.98, 1.01 (2 × 3H, d, J = 6.8, $CH(CH_3)_2$), 1.32 (3H, t, J = 7.1, OCH_2CH_3), 1.35 (3H, d, J = 7.1, C(α)*Me*), 1.78–1.92 (2H, m, C(4)H_A, $CH(CH_3)_2$), 2.04–2.12 (1H, m, C(4)H_B), 2.74–2.78 (1H, m, C(5)*H*), 3.69 (1H, d, J = 15.4, NCH_A), 3.86 (1H, q, J = 7.1, C(α)*H*), 3.89 (1H, d, J = 15.4, NCH_B), 4.20 (2H, q, J = 7.1, OCH_2CH_3), 5.60 (1H, d, J = 15.9, C(2)*H*), 6.78 (1H, app dt, J = 15.9, J = 6.9, C(3)*H*), 7.26–7.51 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3, 20.0, 20.3, 21.0, 31.6, 32.1, 51.9, 58.1, 60.1, 60.8, 121.7, 126.5, 127.1, 127.9, 128.0, 128.2, 128.3, 141.6, 142.9, 149.1, 166.6; *m/z* (APCI) 380 (MH^+, 11%), 276 (59), 105 (100); HRMS (ESI) $C_{25}H_{34}NO_2^+$ requires 380.2590; found 380.2595.

(*R*)-6-Phenylpiperidin-2-one 30[27]

Following *general procedure 5*, $Pd(OH)_2$/C (250 mg), ethyl α,β-unsaturated-δ-amino ester (*E*)-**24** (500 mg) in MeOH (5 mL), and H_2 (5 atm) gave, after purification *via* column chromatography (EtOAc : pentane 10 : 1), the title compound **30** as a colourless amorphous solid (142 mg, 67%); mp 115–117 °C; $[\alpha]_D^{25}$ +58.2 (c = 1.1, $CHCl_3$); ν_{max} (KBr) 3272 (N-H); 1651 (C=O); δ_H (400 MHz, $CDCl_3$) 1.63–1.72 (1H, m, C(5)H_A), 1.74–1.87 (1H, m, C(4)H_A), 1.88–1.98 (1H, m, C(4)H_B), 2.08–2.13 (1H, m, C(5)H_B), 2.37–2.51 (2H, m, C(3)H_2), 4.55 (1H, dd, J = 8.7, J = 4.4, C(6)*H*), 6.03–6.08 (1H, br m, N*H*), 7.27–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.6, 31.3, 32.1, 57.7, 126.0, 127.9, 128.8, 142.5, 172.3; *m/z* (APCI) 176 (MH^+, 100%); HRMS (ESI) $C_{11}H_{14}NO^+$ requires 176.1075; found 176.1082.

(*S*)-6-Methylpiperidin-2-one 31[28]

Following *general procedure 5*, $Pd(OH)_2$/C (250 mg), ethyl α,β-unsaturated-δ-amino ester (*E*)-**26** (500 mg) in MeOH (5 mL), and H_2 (5 atm) gave, after purification *via* column chromatography (EtOAc : pentane 10 : 1), the title compound **31** as a colourless amorphous solid (158 mg, 98%); mp 79–81 °C; $[\alpha]_D^{25}$ +22.7 (c = 0.3, $CHCl_3$); ν_{max} (KBr) 3285 (N-H), 1659 (C=O); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, J = 6.7, C(3)HCH_3), 1.27–1.36 (1H, m, C(5)H_A), 1.62–1.73 (1H, m, C(5)H_B), 1.83–1.91 (2H, m, C(4)H_2), 2.20–2.29 (1H, m, C(3)H_A), 2.32–2.40 (1H, m, C(3)H_B), 3.46–3.51 (1H, m, C(6)*H*), 6.46 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 19.8, 22.7, 30.4, 30.9, 48.7, 172.5; *m/z* (APCI) 114 (MH^+, 100%); HRMS (ESI) $C_6H_{12}NO^+$ requires 114.0919; found 114.0918.

(*R*)-6-*iso*-Propylpiperidin-2-one 32

Following *general procedure 5*, $Pd(OH)_2$/C (250 mg), ethyl α,β-unsaturated-δ-amino ester (*E*)-**28** (500 mg) in MeOH (5 mL), and H_2 (5 atm) gave, after purification by column chromatography (EtOAc : pentane 10 : 1), the title compound **32** as a colourless amorphous solid (181 mg, 97%); mp 75–77 °C; $[\alpha]_D^{25}$ +68.9 (c = 0.4, $CHCl_3$); ν_{max} (KBr) 3235 (N-H), 1660 (C=O); δ_H (400 MHz, $CDCl_3$) 0.92, 0.94 (2 × 3H, d, J = 6.9, $CH(CH_3)_2$), 1.32–1.42 (1H, m, C(5)H_A), 1.60–1.71 (2H, m, C(4)H_A, $CH(CH_3)_2$), 1.81–1.95 (2H, m, C(4)H_B, C(5)H_B), 2.21–2.29 (1H, m, C(3)H_A), 2.36–2.43 (1H, m, C(3)H_B), 3.15–3.20 (1H, m, C(6)*H*), 5.90 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 17.8, 18.0, 20.0, 24.9, 31.4, 32.8, 58.7, 172.8; *m/z* (APCI) 142 (MH^+, 100%); HRMS (ESI) $C_8H_{16}NO^+$ requires 142.1232; found 142.1233.

(*R*)-2-Phenylpiperidine hydrochloride 33

Following *general procedure 6*, $LiAlH_4$ (0.9 mL, 0.86 mmol) and piperidin-2-one **30** (50 mg, 0.29 mmol) in Et_2O (5 mL) gave, after purification *via* column chromatography (DCM : MeOH 20 : 1), the title compound **33** as a colourless amorphous solid (53 mg, 95%); mp 195–197 °C; $[\alpha]_D^{23}$ −2.8 (c = 1.0, MeOH), lit.[22] $[\alpha]_D^{23}$ −3.1 (c = 1.0, MeOH)}; δ_H (400 MHz, $CDCl_3$) 1.46–1.56 (1H, m, C(4)H_A), 1.66–1.70 (1H, m, C(5)H_A), 1.91–2.17 (4H, m, C(3)H_2, C(4)H_B, C(5)H_B), 2.64–2.72 (1H, m, C(6)H_A), 2.99–3.03 (1H, m, C(6)H_B), 3.85–3.88 (1H, m, C(2)*H*), 7.27–7.58 (5H, m, *Ph*), 9.40 (2H, br s, NH_2^+).

(*S*)-2-Methylpiperidine hydrochloride 34

Following *general procedure 6*, $LiAlH_4$ (1.3 mL, 1.33 mmol) and piperidin-2-one **31** (50 mg, 0.44 mmol) in Et_2O (5 mL) gave, after purification *via* column chromatography (DCM : MeOH 20 : 1), the title compound **34** as a colourless amorphous solid (54 mg, 90%); mp 195–197 °C; $[\alpha]_D^{23}$ −3.6 (c = 1.1, EtOH), lit.[23] *ent.* $[\alpha]_D^{23}$ +4.0 (c = 2, EtOH)}; δ_H (400 MHz, $CDCl_3$) 1.32–1.99 (9H, m, C(2)HCH_3, C(3)H_2, C(4)H_2, C(5)H_2), 2.81–2.86 (1H, m, C(6)H_A), 3.10–3.13 (1H, m, C(2)*H*), 3.41–3.45 (1H, m, C(6)H_B), 9.18, 9.56 (2 × 1H, br s, NH_2^+).

(*R*)-2-*iso*-Propylpiperidine hydrochloride 35

Following *general procedure 6*, $LiAlH_4$ (1.1 mL, 1.06 mmol) and piperidin-2-one **32** (50 mg, 0.35 mmol) in Et_2O (5 mL) gave, after purification *via* column chromatography (DCM : MeOH 20 : 1), the title compound **35** as a colourless amorphous solid (55 mg, 95%); mp 168–170 °C; $[\alpha]_D^{24}$ +7.5 (c = 0.5, $CHCl_3$); ν_{max} (KBr) 3400 (NH_2^+); δ_H (400 MHz, $CDCl_3$) 1.10 (6H, app t, J = 7.4, $CH(CH_3)_2$), 1.37–1.47 (1H, m, C(4)H_A), 1.57–1.67 (1H, m, C(3)H_A), 1.76–2.06 (4H, m, C(3)H_B, C(4)H_B, C(5)H_2), 2.17–2.27 (1H, m C$H(CH_3)_2$), 2.75–2.86 (2H, br m, C(2)*H*, C(6)H_A), 3.54–3.57 (1H, m, C(6)H_B), 9.00, 9.35 (2 × 1H, br s, NH_2^+); δ_C (100 MHz, $CDCl_3$) 17.8, 19.7, 22.3, 22.8, 24.7, 30.8, 45.9, 63.2; *m/z* (EI) 127 (100%, M^+); HRMS (EI) $C_8H_{17}N^+$ requires 127.1361; found 127.1361.

(3*S*,α*S*)-*N*-Methoxy-*N*-methyl-3-(*N*′-benzyl-*N*′-α-methylbenzylamino)hexanamide 37

Following *general procedure 1*, *n*-BuLi (23.7 mL, 59.2 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (12.8 mL, 61.1 mmol) in THF (50 mL), and α,β-unsaturated Weinreb amide **36** (6.00 g, 38.2 mmol) in THF (20 mL) gave, after purification *via* column chromatography (pentane : Et_2O 10 : 1), the title compound **37** as a colourless oil (13.5 g, 96%, >95% de); $[\alpha]_D^{24}$ −41.9 (c = 1.0, $CHCl_3$); ν_{max} (film) 1662 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89–0.98 (3H, m, C(6)H_3), 1.23–1.34 (1H, m, C(4)H_A), 1.36–1.52 (2H, m, C(4)H_B, C(5)H_A), 1.38 (3H, d, J = 7.0, C(α)*Me*), 1.64–1.71 (1H, m, C(5)H_B), 1.94–1.99 (1H, m, C(2)H_A), 2.18–2.25 (1H, m, C(2)H_B), 3.08 (3H, s, NCH_3), 3.41 (3H, s, OCH_3), 3.48–3.52 (1H, m, C(3)*H*), 3.59 (1H, d, J = 14.9, N′CH_A), 3.85 (1H, q, J = 7.0, C(α)*H*), 3.88 (1H, d, J = 14.9, N′CH_B), 7.20–7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3, 19.9, 20.4, 33.9, 36.4, 50.2, 51.6, 52.6, 57.7, 60.8, 126.6, 126.7, 128.0, 128.1, 128.2, 128.4, 142.0, 143.2, 173.5; *m/z* (APCI) 369 (MH^+, 100%), 265 (26), 105 (80); HRMS (CI) $C_{23}H_{33}N_2O_2^+$ requires 369.2542; found 369.2545.

(2*Z*,5*S*,α*S*)- and (2*E*,5*S*,α*S*)-Ethyl 5-(*N*-benzyl-*N*-α-methylbenzylamino)oct-2-enoate (*Z*)-39 and (*E*)-38

Following *general procedure 3*, DIBAL-H (8.2 mL, 8.2 mmol), β-amino Weinreb amide **37** (1.50 g, 4.08 mmol) in THF (10 mL), *n*-BuLi (2.0 mL, 4.89 mmol) and triethylphosphono-

acetate (1.0 mL, 4.89 mmol) in THF (5 mL) gave, after purification and separation *via* column chromatography (pentane : Et_2O 80 : 1), (*Z*)-**39** (0.08 g, 5%) as a colourless oil; $[\alpha]_D^{22}$ −24.8 (*c* = 0.4, $CHCl_3$); ν_{max} (film) 1718 (C=O), 1641 (C=C); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, app t, *J* = 6.9, C(8)H_3), 1.27 (3H, t, *J* = 7.3, OCH_2CH_3), 1.33 (3H, d, *J* = 6.9, C(α)*Me*), 1.34–1.68 (4H, m, C(6)H_2, C(7)H_2), 2.49–2.77 (2H, m, C(4)H_2), 3.71 (1H, d, *J* = 14.9, NCH_A), 3.84 (1H, d, *J* = 14.9, NCH_B), 3.95 (1H, q, *J* = 6.9, C(α)*H*), 4.14 (2H, q, *J* = 7.3, OCH_2CH_3), 4.22 (1H, m, C(5)*H*), 5.68 (1H, d, *J* = 11.7, C(2)*H*), 5.87–5.99 (1H, m, C(3)*H*), 7.18–7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3, 18.3, 20.6, 31.0, 35.0, 50.0, 57.0, 57.6, 59.6, 119.6, 126.6, 126.7, 127.9, 128.1, 128.2, 128.4, 142.2, 144.5, 150.0, 166.6; *m*/*z* (APCI) 380 (MH^+, 48%), 276 (93), 105 (100); HRMS (CI) $C_{25}H_{34}NO_2^+$ requires 380.2590; found 380.2586; further elution gave (*E*)-**38** (1.23 g, 80%) as a colourless oil; $[\alpha]_D^{24}$ −18.6 (*c* = 1.2, $CHCl_3$); ν_{max} (film) 1719 (C=O), 1651 (C=C); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, app t, *J* = 7.2, C(8)H_3), 1.34 (3H, t, *J* = 7.3, OCH_2CH_3) and 1.35 (3H, d, *J* = 7.1, C(α)*Me*) overlapping, 1.27–1.39 (2H, m, C(6)H_A, C(7)H_A), 1.46–1.55 (1H, m, C(6)H_B), 1.59–1.69 (1H, m, C(7)H_B), 1.90–2.04 (2H, m, C(4)H_2), 2.84–2.91 (1H, m, C(5)*H*), 3.66 (1H, d, *J* = 14.7, NCH_A), 3.88 (1H, d, *J* = 14.7, NCH_B), 3.91 (1H, q, *J* = 7.1, C(α)*H*), 4.22 (2H, q, *J* = 7.3, OCH_2CH_3), 5.68 (1H, d, *J* = 15.5, C(2)*H*), 6.77 (1H, app dt, *J* = 15.5, *J* = 7.6, C(3)*H*), 7.26–7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3, 19.4, 20.5, 34.6, 35.0, 50.0, 56.0, 57.6, 60.1, 122.1, 126.6, 126.9, 127.8, 128.0, 128.2, 128.3, 141.9, 143.6, 148.3, 166.6; *m*/*z* (APCI) 380 (MH^+, 10%), 276 (29), 105 (100); HRMS (CI) $C_{25}H_{34}NO_2^+$ requires 380.2590; found 380.2589.

(*S*)-6-Propylpiperidin-2-one 40

Following *general procedure 5*, $Pd(OH)_2$/C (250 mg), ethyl α,β-unsaturated-δ-amino ester (*E*)-**38** (500 mg) in MeOH (5 mL), and H_2 (5 atm) gave, after purification *via* column chromatography (EtOAc : pentane 10 : 1), the title compound **40** as a colourless amorphous solid (183 mg, 98%); mp 58–60 °C; $[\alpha]_D^{22}$ +18.1 (*c* = 0.6, $CHCl_3$), ν_{max} (KBr) 3208 (N-H), 1665 (C=O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, m, C(6)$HCH_2CH_2CH_3$), 1.33–1.48 (6H, m, C(6)$HCH_2CH_2CH_3$, C(5)H_2), 1.63–1.73 (1H, m, C(4)H_A), 1.85–1.94 (1H, m, C(4)H_B), 2.24–2.33 (1H, m, C(3)H_A), 2.36–2.43 (1H, m, C(3)H_B), 3.29–3.33 (1H, m, C(6)*H*), 5.76–5.79 (1H, br m, N*H*); δ_C (100 MHz, $CDCl_3$) 13.9, 18.5, 19.8, 28.5, 31.3, 39.1, 52.9, 172.3; *m*/*z* (APCI) 142 (MH^+, 100%); HRMS (CI) $C_8H_{15}NO^+$ requires 142.1232; found 142.1233.

(*S*)-2-Propylpiperidine hydrochloride [(*S*)-coniine hydrochloride] 41

Following *general procedure 6*, $LiAlH_4$ (1.1 mL, 1.06 mmol) and piperidin-2-one **40** (50 mg, 0.35 mmol) in Et_2O (5 mL) gave, after purification *via* column chromatography (DCM : MeOH 20 : 1), the title compound **41** as a colourless amorphous solid (52 mg, 90%); mp 217–219 °C; $[\alpha]_D^{23}$ +9.1 (*c* = 0.6, EtOH), lit.[26] $[\alpha]_D^{23}$ +9.4 (*c* = 0.3, EtOH)}; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* = 7.3, C(2)$HCH_2CH_2CH_3$), 1.37–2.01 (10H, m, C(2)$HCH_2CH_2CH_3$, C(3)H_2, C(4)H_2, C(5)H_2), 2.75–2.85 (1H, m, C(6)H_A), 2.90–3.00 (1H, m, C(6)H_B), 3.40–3.50 (1H, m, C(2)*H*), 9.18, 9.52 (2 × 1H, br s, NH_2^+).

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