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Asymmetric synthesis of cyclic β-amino acids and cyclic amines via sequential diastereoselective conjugate addition and ring closing metathesis

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Abstract—Diastereoselective conjugate addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide to a range of α,β-unsaturated esters followed by ring closing metathesis is used to afford efficiently a range of substituted cyclic β-amino esters in high d.e. Alternatively, conjugate addition to α,β-unsaturated Weinreb amides, functional group conversion and ring closing metathesis affords cyclic amines in high d.e. The further application of this methodology to the synthesis of a range of carbocyclic β-amino esters via conjugate addition, enolate alkylation and ring closing metathesis is also described. Application of this methodology affords, after deprotection, (*S*)-homoproline, (*S*)-homopipecolic acid, (*S*)-coniine and (1*S*,2*S*)-*trans*-pentacin. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The metal-catalysed exchange of the alkylidene groups of two olefins has attracted enormous attention in the last decade,[1] predominantly since the pioneering studies of Schrock[2] and Grubbs,[3] who detailed the first synthetic applications of the general functional group tolerant molybdenum and ruthenium based alkylidene complexes $PhC(Me)_2CH{=}Mo{=}N[2,6\text{-}(^iPr)_2C_6H_3]\{[OCMe(CF_3)_2]_2\}$ and $PhCH{=}Ru(PCy_3)_2Cl_2$ **1**, respectively. The stability and reactivity of such complexes has allowed ring closing metathesis to be used widely within organic synthesis,[4] with specific application to the synthesis of a range of nitrogen containing heterocyclic compounds,[5] alkaloids[6] and amino acid derivatives[7] being well documented.[8] These studies have demonstrated that the efficiency of a given metathesis reaction is highly dependent upon the environment around the reaction centre, particularly if a chelating or co-ordinating substituent is in close proximity to one of the C=C double bonds undergoing reaction. For instance, both Rutjes[9] and Maier[10] have shown that the efficacy of ring closing metathesis of *N*-containing substrates **2**–**4** and **5**–**7** with Grubbs catalyst **1** is highly dependent upon the nature of the *N*-protecting groups. Changes in both the conformational and basic character of the nitrogen atom, as well as an increase in steric bulk affect markedly the ring closure (Fig. 1).

Previous investigations from our laboratory have shown that lithium (*R*)-*N*-allyl-*N*-α-methylbenzylamide **8** undergoes highly diastereoselective conjugate addition reactions to α,β-unsaturated esters to give tertiary β-amino esters with high levels of predictable diastereoselectivity.[11] Differential

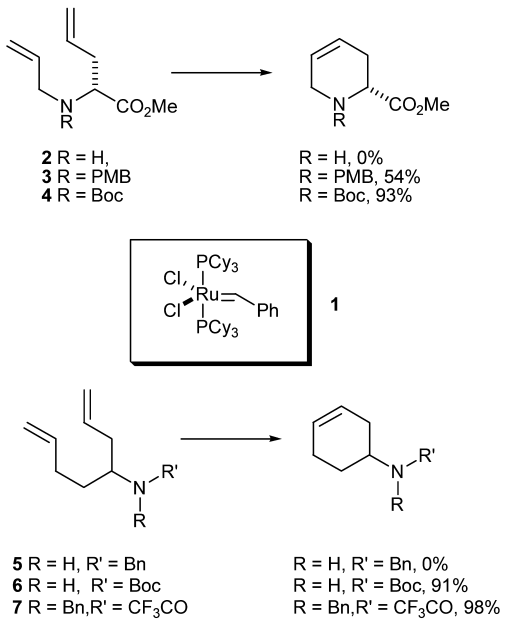

Figure 1.

Keywords: lithium amide; conjugate addition; ring closing metathesis.

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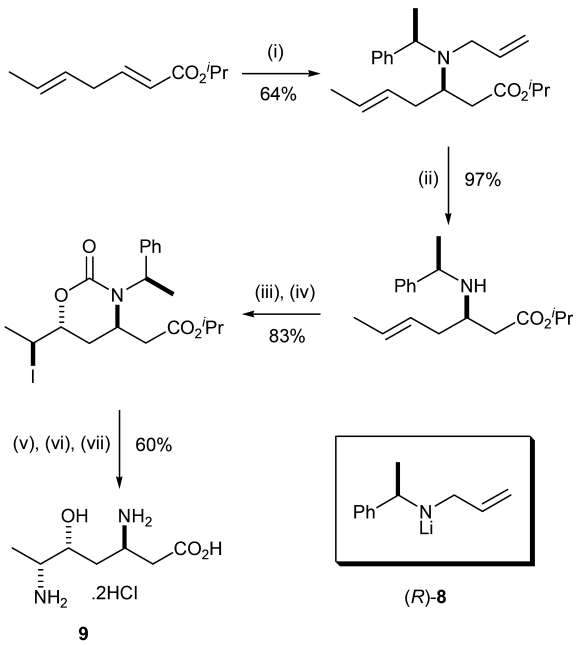


Scheme 1. *Reagents and conditions*: (i) (*R*)-**8**, THF, −78°C; (ii) $Pd(PPh_3)_4$, DCM, *N*,*N*-dimethylbarbituric acid; (iii) $(Cbz)_2O$, DCM; (iv) I_2, DCM, 0°C; (v) NaN_3, DMF; (vi). H_2, Pd/C; (vii). 5N, HCl, △.

N-deprotection via deallylation through either rhodium[12] or palladium catalysis[13] allows further functionalisation, as demonstrated by the synthesis of the key β-amino acid **9** of Sperabillin B and D (Scheme 1).[14]

As a further application of this versatile methodology, we report herein upon the scope of the diastereoselective conjugate addition of lithium amide (*S*)-**8** for the formation of a range of homochiral dienes. Application of this methodology enables the limitations of alkene substitution and ring size upon the efficiency of ring closing metathesis to be evaluated via the synthesis of a range of heterocyclic and carbocyclic derivatives. Part of this work has been communicated previously.[15]

2. Results and discussion

2.1. Preparation of homochiral dienes via conjugate addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide to α,β-unsaturated acceptors

Initial investigations were directed toward the synthesis of a range of homochiral dienes via conjugate addition of lithium amide (*S*)-**8** to a variety of α,β-unsaturated acceptors, in which direct functionalisation of the *N*-allyl group of lithium amide (*S*)-**8** could be achieved via ring closing metathesis (Fig. 2).[16]

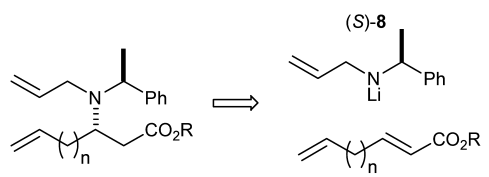
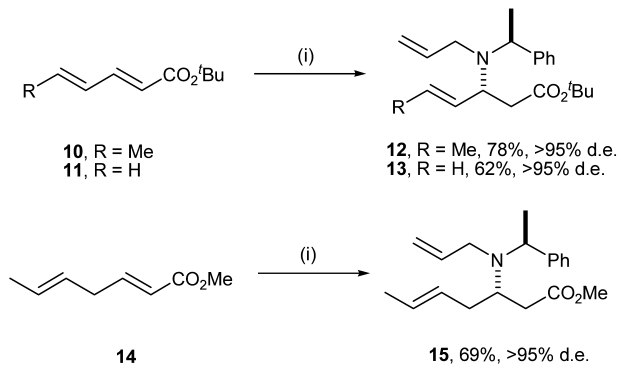


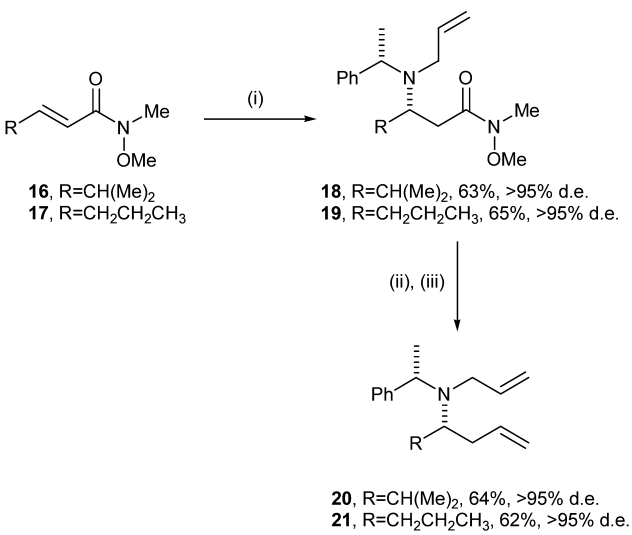
Figure 2.



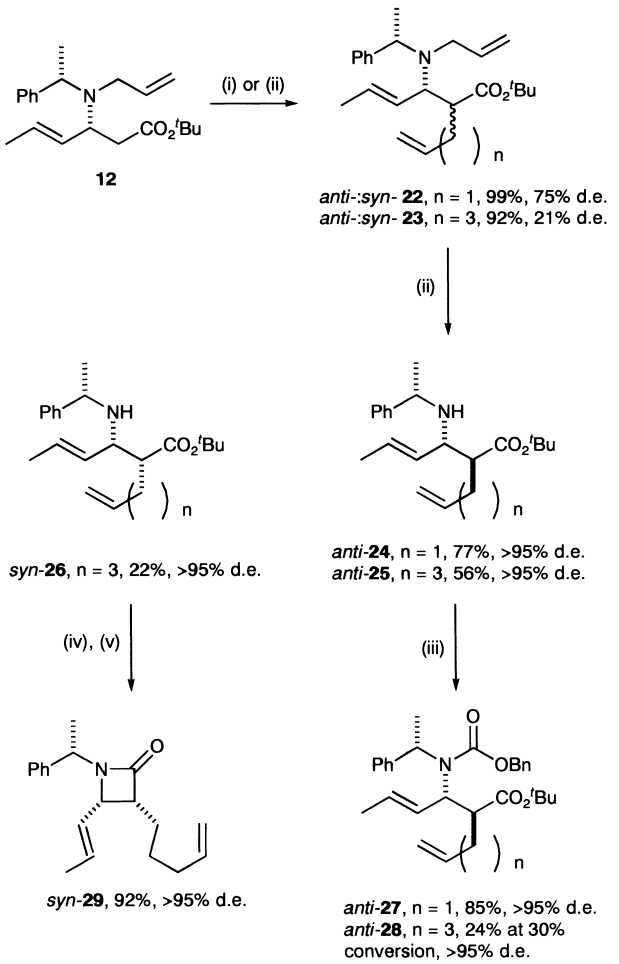
Scheme 2. *Reagents and conditions*: (i) (*S*)-**8**, THF, −78°C.

To evaluate this methodology, conjugate addition of lithium amide (*S*)-**8** to both (*E*,*E*)-*tert*-butyl hexa-2,4-dieneoate **10** and (*E*)-*tert*-butyl penta-2,4-dieneoate **11** gave *N*-allyl β-amino esters (3*R*,α*S*,4*E*)-**12**[17] and (3*R*,α*S*)-**13** in 78 and 62% yield, respectively, and in >95% d.e. in each case. In a similar fashion, conjugate addition of lithium amide (*S*)-**8** to (*E*,*E*)-methyl heptan-2,5-dieneoate **14** gave (3*S*,5*E*,α*S*)-methyl 3-(*N*-allyl-*N*-α-methylbenzylamino)hept-5-enoate **15** in 69% yield and >95% d.e. (Scheme 2).

Having prepared homochiral dienes via conjugate addition of lithium *N*-allyl amide (*S*)-**8** to α,β-unsaturated acceptors, the use of α,β-unsaturated Weinreb amides in this protocol was probed. It was envisaged that conjugate addition, combined with subsequent amide functional group conversion would enable an alternative and facile synthesis of dienes for ring closing metathesis. To test the viability of this procedure, conjugate addition of lithium amide (*S*)-**8** to (*E*)-*N*-methoxy-*N*-methyl 4-methyl-pent-2-eneamide **16** or (*E*)-*N*-methoxy-*N*-methyl hex-2-eneamide **17** gave β-amino esters (3*R*,α*S*)-**18** and (3*S*,α*S*)-**19** in 63 and 65% yield, respectively, and in >95% d.e. in each case. Reduction of β-amino Weinreb amides (3*R*,α*S*)-**18** and (3*S*,α*S*)-**19** with DIBAL-H and treatment of the crude reaction mixture with sodamide and triphenylphosphonium methylbromide afforded (4*R*,α*S*)-**20** and (4*S*,α*S*)-**21** in 64 and 62% yield, respectively (Scheme 3).



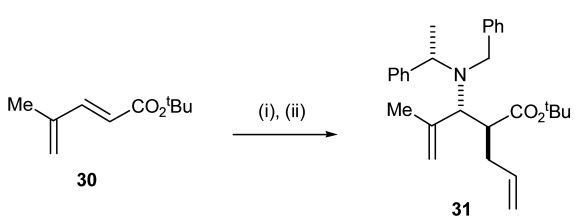
Scheme 3. *Reagents and conditions*: (i) (*S*)-**8**, THF, −78°C; (ii) DIBAL-H, THF, −78°C; (iii) Ph_3PCH_3Br, $NaNH_2$, DCM, 0°C to rt.



Scheme 4. *Reagents and conditions*: (i) LDA, THF, −78°C; then allyl bromide, −78°C to rt; (ii) LDA, THF, −78°C; then 1-bromopent-4-ene, −78°C to rt; (iii) $(PPh_3)_3RhCl$, $MeCN/H_2O$, △; (iv) $(Cbz)_2O$; (v) TFA, DCM (1:1), rt; (vi) $(PyS)_2$, MeCN, PPh_3, △.

2.2. Preparation of homochiral dienes via conjugate addition/alkylation

A strategy for the synthesis of dienes involving enolate alkylation was next probed, with deprotonation of *N*-allyl β-amino ester (3*R*,α*S*)-**12** with LDA and alkylation with allyl bromide giving an inseparable mixture of *anti*- and *syn*-diastereoisomers **22** in 75% d.e. and 99% yield. Similarly, alkylation of β-amino ester (3*R*,α*S*)-**12** with 1-bromopent-4-ene gave an inseparable mixture of *anti*- and *syn*-diastereoisomers **23** in 21% d.e. and 92% yield. In each case the *anti*-configuration of the major diastereoisomer was assigned by analogy to the selectivity previously reported for alkylation of β-amino enolates.[18] N-Deallylation of the mixtures of diastereoisomers **22** and **23** with Wilkinson's catalyst produced a mixture of secondary amines, which were separable by column chromatography, providing the major diastereoisomer of α-allylated β-amino ester *anti*-**24** in 77% yield and >95% d.e. from **22**, and furnishing the major diastereoisomer *anti*-**25** in 56% yield and >95% d.e., and the minor diastereomer *syn*-**26** in 22% yield and >95% d.e. from **23**. As previous investigations have shown that unprotected amines may have a deleterious effect upon the efficiency of ring closing metathesis,[9,10] β-amino esters **24** and **25** were *Z*-protected, furnishing carbamates **27** and **28**, respectively, while the minor diastereoisomer *syn*-**26** was subjected to ester deprotection and cyclisation using Ohno's conditions,[19] giving the dieneyl β-lactam **29** in 92% yield (Scheme 4).



Scheme 5. *Reagents and conditions*: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78°C; (ii) allyl bromide (1.5 equiv.).

In a similar manner, tandem conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to (*E*)-*tert*-butyl 4-methyl-penta-2,4-dieneoate **30** and alkylation with allyl bromide gave a 1.1:1 mixture of *anti*- to *syn*-diastereoisomers which differed in configuration at C(2), from which the major diastereoisomer *anti*-**31** was isolated in 36% yield as a single diastereoisomer by column chromatography and recrystallisation (Scheme 5). The relative *anti*-configuration within β-amino ester **31** was confirmed by X-ray crystallographic analysis, with the absolute (2*S*,3*R*,α*S*)-configuration confirmed relative to the known configuration of the *N*-α-methylbenzyl group (Fig. 3).

2.3. Ring closing metathesis of homochiral dienes

Having prepared a range of homochiral dienes, their susceptibility to ring closing metathesis was investigated, initially concentrating upon treatment of β-amino esters **12** and **13** with Grubbs' ruthenium alkylidene catalyst $PhCH{=}Ru(PCy_3)_2Cl_2$ **1**. Each furnished the desired *N*-α-methylbenzyl-protected pyrrolidine β-amino ester (2*R*,α*S*)-**32** in comparable 77 and 76% yields respectively, and as a single diastereoisomer in each case, indicating that no epimerisation had taken place during the ring closing metathesis protocol. Alternative ring closing metathesis

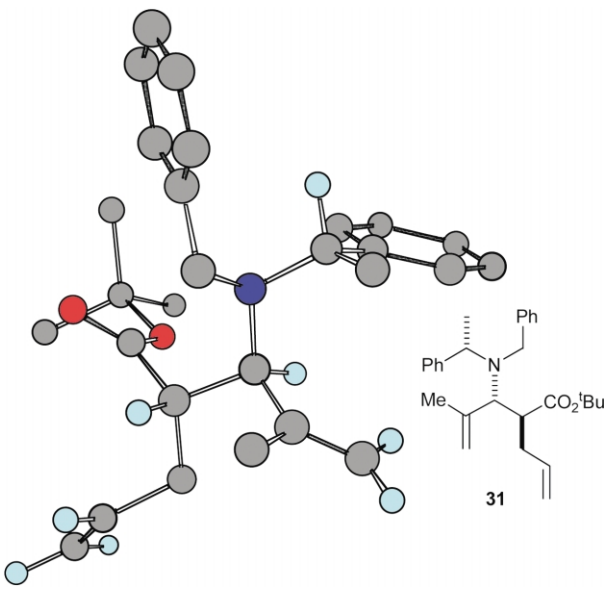
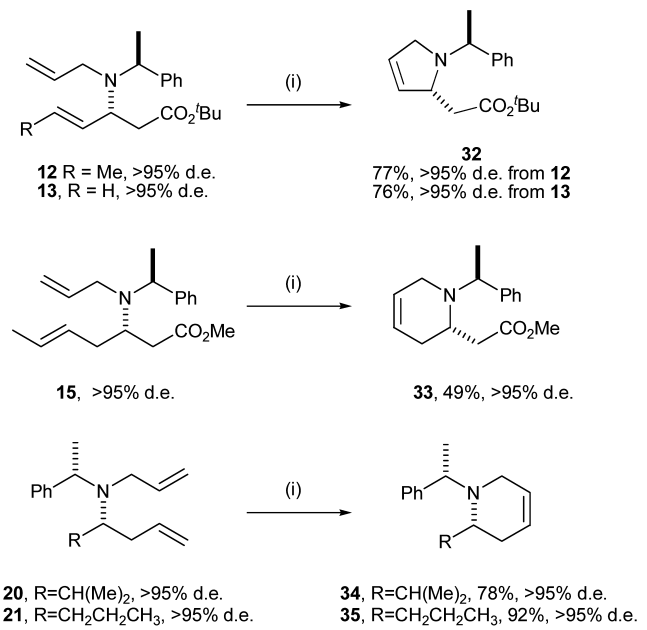
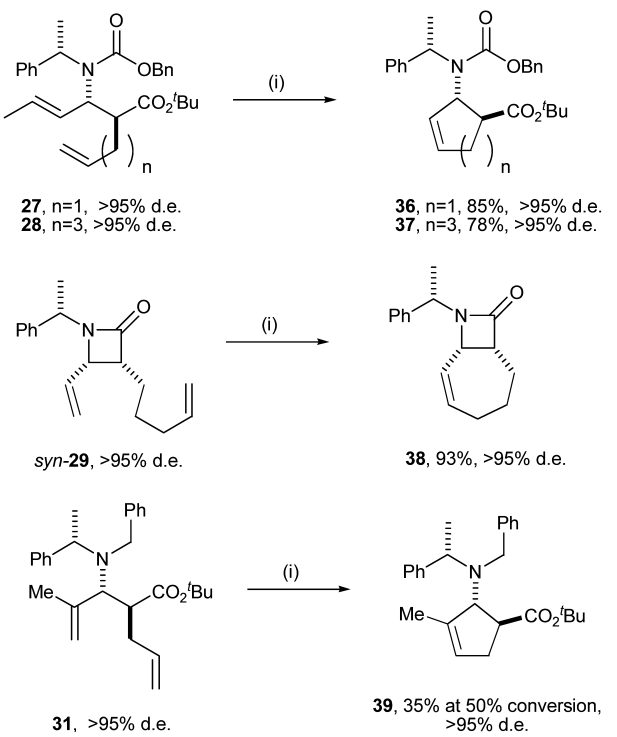


Figure 3. Chem 3D representation of the X-ray crystal structure of (2*S*,3*R*,α*S*)-**31**.



Scheme 6. *Reagents and conditions*: (i) 4 mol% $RuCl_2(=CHPh)(PCy_3)_2$, DCM, △, 12 h.



Scheme 7. *Reagents and conditions*: (i) 4 mol% $RuCl_2(=CHPh)(PCy_3)_2$, DCM, △, 12 h.

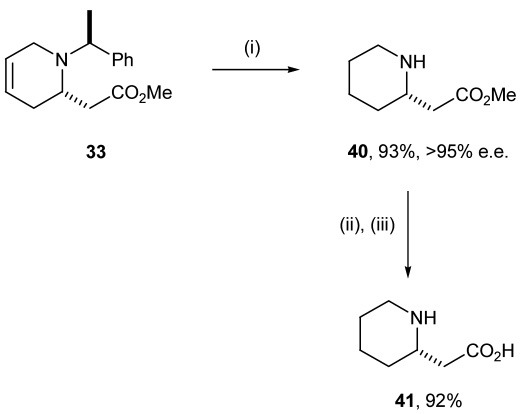
catalysts showed lower reactivity upon reaction with β-amino ester **12**, the Nugent[20] catalyst failing to generate any of the desired β-amino ester **32**, while treatment with the Schrock catalyst $PhC(Me)_2CH{=}Mo{=}N[2,6\text{-}(^iPr)_2C_6H_3]\{[OCMe(CF_3)_2]_2\}$[2] produced 60% conversion to **32**. Grubbs' ruthenium alkylidene catalyst **1** was therefore used in all further studies, with β-amino ester **15** furnishing the piperidine β-amino ester (2*S*,α*S*)-**33** in 49% yield and in >95% d.e., while treatment of dienes (4*R*,α*S*)-**20** and (4*S*,α*S*)-**21** provided the cyclic amines **34** and **35** in 78 and 92% yield, respectively, and in >95% d.e. in each case (Scheme 6).

Having demonstrated the use of Grubbs' alkylidene catalyst for the synthesis of *N*-protected heterocyclic amino acids and amines, application to the synthesis of carbocyclic β-amino ester derivatives was attempted. Treatment of *N*-*Z* β-amino esters **27** and **28** with 4 mol% catalyst **1** proceeded efficiently, giving the desired five and seven-membered cyclic β-amino esters **36** and **37** in 85 and 78% yield, respectively, and as single diastereoisomers in each case. Treatment of β-lactam **29** with alkylidene **1** similarly proceeded efficiently, giving the bicyclic β-lactam template **38** in 93% yield as a single diastereoisomer, although attempted ring closure of β-amino ester **31** proved difficult to drive to completion, furnishing the desired β-amino ester template **39** in 35% yield at 50% conversion, even after addition of further catalyst. Similar results regarding the efficiency of ring closing metathesis of 1,1′-alkenes with catalyst **1** have been noted in the literature (Scheme 7).[21]

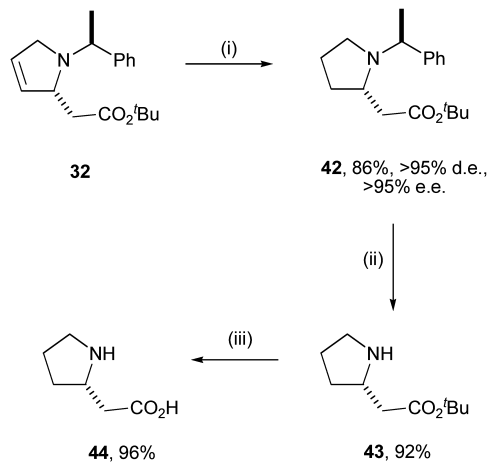
2.4. Deprotection: synthesis of (*S*)-homopipecolic acid, (*S*)-homoproline, (*S*)-coniine and (1*S*,2*S*)-*trans*-pentacin hydrochloride

Having demonstrated that the combination of lithium amide conjugate addition and ring closing metathesis allows access to a diverse range of heterocyclic and carbocyclic systems, methodology for the efficient deprotection of the products of ring closing metathesis was desired. Deprotection of β-amino ester **33** to (*S*)-homopipecolic acid **41**[22] was the initial target of these studies, with *N*-deprotection via catalytic hydrogenation affording β-amino ester **40** in 93% yield and >95% e.e. (as shown by ^1H NMR spectroscopic analysis in the presence of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol and comparison with an authentic racemic standard) indicating that racemisation does not occur under the hydrogenolytic reaction conditions. Subsequent ester hydrolysis and ion exchange chromatography gave (*S*)-homopipecolic acid **41** {$[\alpha]_D^{26}=+24.0$ (*c* 0.87, H_2O); lit.[23] $[\alpha]_D=+22.1$ (*c* 0.6, H_2O)} in 92% yield (Scheme 8).

Deprotection of β-amino ester (2*R*,α*S*)-**32** to (*S*)-homoproline **44**[24] was successfully achieved via alkene hydrogenation with Wilkinson's catalyst, furnishing *N*-α-methylbenzyl β-amino ester **42** in 86% yield and as a single



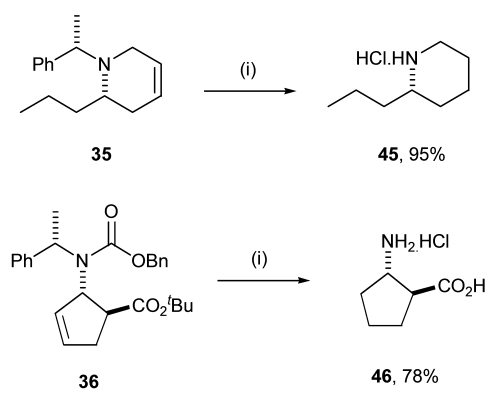
Scheme 8. *Reagents and conditions*: (i) 2 M HCl; (ii) Dowex 50WX8-200.



Scheme 9. *Reagents and conditions*: (i) $(PPh_3)_3RhCl$, H_2 (2 atm), MeCN, rt; (ii) $Pd(OH)_2$ on C, H_2 (1 atm), MeOH–H_2O–AcOH (40:4:1), rt; (iii) HCl (aq) then Dowex 50WX8-200.

diastereoisomer in >95% e.e.[25] *N*-benzyl deprotection via hydrogenolysis furnished β-amino ester **43** in 92% yield, with ester hydrolysis affording (*S*)-homoproline **44** {$[\alpha]_D^{23}$=+3.4 (*c* 1.0, H_2O); lit.[26] $[\alpha]_D^{25}$=+4.0 (*c* 1.0, H_2O)} in excellent yield after purification by ion exchange chromatography (Scheme 9).

Further applications of this hydrogenolytic deprotection were demonstrated via the synthesis of (*S*)-coniine **45**,[27] a simple cyclic alkaloid from *conium-maculatum* (poison hemlock),[28] and (1*S*,2*S*)-*trans*-pentacin **46**, oligomers of which show secondary structure in both solution and the solid state.[29] Thus, hydrogenation of *N*-protected cyclic amine **35** and treatment with HCl, furnished (*S*)-coniine hydrochloride **45** in 95% yield, with specific rotation {$[\alpha]_D^{21}$=+8.3 (*c* 0.7, EtOH); lit, $[\alpha]_D^{25}$=+9.4 (*c* 0.32, EtOH);[30] $[\alpha]_D^{25}$=+8.1 (*c* 0.6, EtOH)[31]} and spectroscopic properties consistent with those of the literature. Similarly, exhaustive hydrogenation and ester hydrolysis of β-amino ester **36** afforded *trans*-pentacin hydrochloride **46** as a single diastereoisomer with spectroscopic properties consistent with those of the literature {$[\alpha]_D$=+46.4 (*c* 1.04, H_2O), lit.[32] *ent* $[\alpha]_D$=−50.7 (*c* 0.75, H_2O)} (Scheme 10).[33]



Scheme 10. *Reagents and conditions*: (i) 10% Pd/C, H_2 (5 atm), MeOH, rt; then HCl.

3. Conclusion

A strategy involving diastereoselective conjugate addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide to an α,β-unsaturated ester or amide, followed by ring closing metathesis has been successfully developed. Application of this protocol allows the asymmetric synthesis of the amine (*S*)-coniine **45**, the heterocyclic β-amino acids (*S*)-homoproline **44** and (*S*)-homopipecolic acid **41**, and carbocyclic (1*S*,2*S*)-*trans*-pentacin **46**. Further applications of the diastereoselective conjugate addition of homochiral lithium amides, coupled with ring closing metathesis for the asymmetric synthesis of a variety of natural products are currently underway within our laboratory.

4. Experimental

4.1. General experimental

All reactions involving moisture sensitive reagents were performed under an atmosphere of dry nitrogen or argon via standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. THF was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. Water was distilled. BuLi was used as a solution in hexanes (Aldrich) at the molarity stated. $PhCH{=}Ru(PCy_3)_2Cl_2$ was used as supplied (Lancaster). 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. Flash column chromatography was performed on Kieselgel 60 silica or neutral alumina. Nuclear magnetic resonance spectra were recorded on either a Bruker AMX 500 spectrometer (^{1}H: 500 MHz and ^{13}C: 126 MHz), Bruker DPX 400 spectrometer (^{1}H: 400 MHz and ^{13}C: 100 MHz) or a Bruker DPX 200 spectrometer (^{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. Specific optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g/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 the Dyson Perrins Laboratory, Oxford or the Inorganic Chemistry Laboratory, Oxford.

4.2. Representative procedure 1

To a solution of β-amino ester (6 mmol) in DCM (200 mL) was added ruthenium alkylidene **1** (0.25 mmol, 4 mol%) under argon flow and stirred at reflux under argon for 12 h. The solution was concentrated in vacuo and purified by column chromatography.

4.2.1. (3*R*,4*E*,α*S*)-Methyl 3-(*N*-allyl-*N*-α-methylbenzylamino)-hept-4-enoate 12. Following the literature procedure,[34] (*S*)-*N*-allyl-*N*-α-methylbenzylamine (3.0 g, 18.5 mmol) in THF (30 mL), *n*-BuLi (1.63 M, 10.5 mL, 17.0 mmol) and **10** (2.0 g, 14.2 mmol) in THF (10 mL) gave, after purification by column chromatography on silica gel, (5% Et_2O/40–60 petrol), **12** as clear pale yellow oil (2.9 g, 69%); $[\alpha]_D^{23}$=+6.4 (*c* 1.32, $CHCl_3$), ν_{max}/cm^{-1} (film) 1728 s(C=O); δ_H ($CDCl_3$, 500 MHz), 7.34–7.20 (5H, m, *Ph*), 5.91–5.81 (1H, m, NCH_2CHCH_A), 5.48–5.37 (2H, m, C(5)*H*=C(6)*H*), 5.15 (1H, dd, *J*=15.5, 1.7 Hz, NCH_2CHCH_B), 5.05 (1H, dd, *J*=10.1, 1.6 Hz, NCH_2CHCH_2), 4.00 (1H, q, *J*=6.8 Hz, C(α)*H*), 3.57 (3H, s, O*Me*), 3.45–3.38 (1H, m, C(3)*H*), 3.23 (1H, dd, *J*=15.2, 6.2 Hz, $NCHHCHCH_2$), 3.16 (1H, dd, *J*=15.2, 6.2 Hz, $NCHHCHCH_2$), 2.32–2.21 (3H, m, $C(2)H_2$ and $C(4)H_A$), 2.02–1.95 (1H, m, $C(4)H_B$), 1.67 (3H, d, *J*=5.3 Hz, $C(7)H_3$), 1.39 (3H, d, *J*=6.8 Hz, C(α)*Me*); δ_C ($CDCl_3$, 126 MHz), 173.1 (*C*O), 144.8 (*Ph*$_{ipso}$), 138.8 (NCH_2CH), 128.7, 128.0, 127.6, 126.9, 126.6 (*Ph* and *C*(5)H=*C*(6)H), 115.5 (NCH_2CHCH_2), 57.8 (O*Me*), 55.5 (*C*(α)H), 51.2 (*C*(3)H), 48.9 (NCH_2), 37.4 ($C(2)H_2$), 35.8 ($C(4)H_2$), 19.4 ($C(7)H_3$), 18.8 (C(α)*Me*); *m*/*z* (APCI$^+$), 316 (MH^+, 100%), 260 ($MH^+-C_4H_8$, 55%); HRMS, $C_{20}H_{30}NO_2$ requires 316.2277, found 316.2274.

4.2.2. (3*R*,α*S*)-*tert*-Butyl 3-(*N*-allyl-*N*-α-methylbenzylamino)-pent-4-enoate 13. Following the literature procedure,[34] (*S*)-*N*-allyl-*N*-α-methylbenzylamine (4.5 g, 28.2 mmol) in THF (40 mL), *n*-BuLi (1.60 M, 16.4 mL, 26.3 mmol) and **11** (2.9 g, 18.8 mmol) in THF (25 mL) gave, after purification by column chromatography on silica gel, (5% Et_2O/40–60 petrol) **13** as a clear pale yellow oil (3.65 g, 62%); $[\alpha]_D^{26}$=+8.3 (*c* 1.04, $CHCl_3$); ν_{max}/cm^{-1} (film) 1730 s(C=O); δ_H ($CDCl_3$, 500 MHz), 7.42–7.21 (5H, m, *Ph*), 5.96–5.79 (2H, m, NCH_2CHCH_2 and C(4)*H*), 5.18–5.03 (4H, m, NCH_2CHCH_2 and $C(5)H_2$), 4.06 (1H, q, *J*=6.8 Hz, C(α)*H*), 3.98–3.93 (1H, m, C(3)*H*), 3.18 (2H, app d, *J*=6.2 Hz, NCH_2), 2.45 (1H, dd, *J*=14.5, 6.5 Hz, $C(2)H_A$), 2.34 (1H, dd, *J*=14.5, 8.2 Hz, $C(2)H_B$), 1.48 (9H, s, $C(CH_3)_3$), 1.42 (3H, d, *J*=6.8 Hz, C(α)*Me*); δ_C ($CDCl_3$, 126 MHz), 171.1 (CO_2), 144.9 (*Ph*$_{ipso}$), 138.8, 138.1 (*C*(4)H and NCH_2CH), 128.0, 127.7, 126.6 (*Ph*), 115.8, 115.6 ($C(5)H_2$ and NCH_2CHCH_2), 79.9 ($C(CH_3)_3$), 57.5, 57.3 (*C*(α)H and $NCHCH_2$), 49.6 (NCH_2), 38.9 ($C(2)H_2$), 28.0 ($C(CH_3)_3$), 18.8 (C(α)*Me*); *m*/*z* (APCI$^+$), 316 (MH^+, 100%), 260 ($MH^+-C_4H_8$, 55%); HRMS, $C_{20}H_{30}NO_2$ requires 316.2277, found 316.2274.

4.2.3. (3*S*,5*E*,α*S*)-Methyl 3-(*N*-allyl-*N*-α-methylbenzylamino)hept-5-enoate 15. Following the literature procedure,[34] (*S*)-*N*-allyl-*N*-α-methylbenzylamine (3.0 g, 18.5 mmol) in THF (30 mL), *n*-BuLi (1.63 M, 10.5 mL, 17.1 mmol) and **11** (2.0 g, 14.2 mmol) in THF (10 mL) gave, after purification by column chromatography on silica gel, (5% Et_2O/40–60 petrol) **13** as a clear pale yellow oil (2.9 g, 69%); $[\alpha]_D^{23}$=+6.4 (*c* 1.3, $CHCl_3$), ν_{max}/cm^{-1} (film) 1728 s(C=O); δ_H ($CDCl_3$, 500 MHz), 7.34–7.20 (5H, m, *Ph*), 5.91–5.81 (1H, m, NCH_2CHCH_2), 5.48–5.37 (2H, m, C(5)*H*, C(6)*H*), 5.17–5.13 (1H, dd, *J*=15.5, 1.7 Hz, NCH_2CHCHH), 5.07–5.04 (1H, dd, *J*=10.1, 1.7 Hz, NCH_2CHCHH), 4.02–3.97 (1H, q, *J*=6.8 Hz, C(α)*H*), 3.57 (3H, s, O*Me*), 3.45–3.38 (1H, m, C(3)*H*), 3.26–3.21 (1H, dd, *J*=15.2, 6.2 Hz, $NCHHCHCH_2$), 3.19–3.13 (1H, dd, *J*=15.2, 6.2 Hz, $NCHHCHCH_2$), 2.32–2.21 (3H, m, $C(2)H_2$ and $C(4)H_A$), 2.02–1.95 (1H, m, $C(4)H_B$), 1.68–1.66 (3H, d, *J*=5.3 Hz, $C(7)H_3$), 1.40–1.38 (3H, d, *J*=6.9 Hz, C(α)*Me*); δ_C ($CDCl_3$, 50 MHz), 173.5 (*C*O), 145.1 (*Ph*$_{ipso}$), 139.2, (NCH_2CH), 129.0 (*C*(5)H), 128.2, 127.8 (*Ph*$_{o\text{-},m\text{-}}$), 127.2, 126.8 (*Ph*$_{p\text{-}}$, *C*(6)H), 115.7 (NCH_2CHCH_2), 57.8 (*C*(α)H), 55.5 (*C*(3)H), 51.3 (O*Me*), 48.9 (NCH_2), 37.4, 35.8 ($C(2)H_2$, $C(4)H_2$), 19.4 (C(α)*Me*), 17.9 ($C(7)H_3$); HRMS, $C_{19}H_{27}NO_2$ requires 302.2120, found 302.2119.

4.2.4. (*E*)-*N*-Methoxy-*N*-methyl 4-methyl-pent-2-enamide 16. Isobutyraldehyde (0.50 mL, 5.51 mmol) was added to a solution of *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene) acetamide (2.00 g, 5.51 mmol) in DCM (20 mL) was and stirred at rt for 24 h before concentration in vacuo and purification by column chromatography on silica gel, (5% Et_2O–pentane) to afford **16** as a pale yellow oil (0.80 g, 92%); ν_{max}/cm^{-1} (film) 1664, 1637 s(C=O); δ_H ($CDCl_3$, 400 MHz), 6.88 (1H, dd, *J*=15.5, 6.9 Hz, C(3)*H*), 6.28 (1H, d, *J*=15.5 Hz, C(2)*H*), 3.64 (3H, s, O*Me*), 3.17 (3H, s, N*Me*), 2.45–2.40 (1H, m, Me_2CH), 1.02–1.00 (6H, d, *J*=6.8 Hz, Me_2CH); δ_C ($CDCl_3$, 126 MHz), 167.2 (*C*O), 153.9 (C(3)H), 115.8 (C(2)H), 61.5 (O*Me*), 32.2 (Me_2CH), 31.1 (N*Me*), 21.4 (Me_2CH); *m*/*z* (APCI$^+$), 158 (MH^+, 100%); HRMS, $C_8H_{16}NO_2$ requires 158.1181, found: 158.1187.

4.2.5. (*E*)-*N*-Methoxy-*N*-methyl hex-2-enamide 17. Butyraldehyde (0.81 mL, 9.05 mmol) was added to a solution of *N*-methoxy-*N*-methyl 2-(triphenylphosphoranylidene) acetamide (3.3 g, 9.05 mmol) in DCM (20 mL) and stirred at rt for 12 h before concentration in vacuo. Purification by column chromatography on silica gel, (5% Et_2O/40–60 petrol) gave **17** (0.68 g, 48%) as a colourless oil and as single diastereoisomer; ν_{max}/cm^{-1} (film) 1663 s(C=O), 1635 (C=C); δ_H ($CDCl_3$, 200 MHz), 6.99–6.85 (1H, m, C(3)*H*), 6.35 (1H, dt, *J*=15.5, 1.4 Hz, C(2)*H*), 3.65 (3H, s, O*Me*), 3.19 (3H, s, N*Me*), 2.22–2.11 (2H, m, $C(4)H_2$), 1.54–1.36 (2H, m, $C(5)H_2$), 0.92–0.85 (3H, m, $C(6)H_3$); δ_C ($CDCl_3$, 50 MHz), 167.0 (*C*O), 147.6 (*C*(3)H), 118.7 (*C*(2)H), 61.5 (O*Me*), 34.4 ($C(4)H_2$), 32.2 (N*Me*), 21.5 ($C(5)H_2$), 13.6 ($C(6)H_3$); *m*/*z* (APCI$^+$), 158 (MH^+, 100%); HRMS, $C_8H_{16}NO_2$ requires 158.1181, found 158.1188.

4.2.6. (3*R*,α*S*)-*N*-Methoxy-*N*-methyl 3-(*N*-allyl-*N*-α-methylbenzylamino)-4-methyl-pentanamide 18. Following the literature procedure,[34] (*S*)-*N*-allyl-*N*-α-methylbenzylamine (1.14 g, 7.1 mmol) in THF (30 mL), *n*-BuLi (1.60 M, 4.1 mL, 6.6 mmol) and **16** (795 mg, 5.1 mmol) in THF (5 mL) gave, after purification by column chromatography on silica gel, (20% Et_2O/40–60 petrol), **18** as a pale yellow oil (1.0 g, 63%); $[\alpha]_D^{23}$=+8.0 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} (film) 1664 s(C=O); δ_H ($CDCl_3$, 500 MHz), 7.33–7.16 (5H, m, *Ph*), 5.94–5.86 (1H, m, NCH_2CHCH_2),

5.24 (1H, dd, J=17.3, 1.4 Hz, NCH_2CHCHH), 5.10 (1H, dd, J=10.1, 1.4 Hz, NCH_2CHCHH), 3.94 (1H, q, J=7.1 Hz, C(α)*H*), 3.43 (3H, s, O*Me*), 3.33 (1H, app. dt, J=8.2, 3.1 Hz, $NCHCH_2$), 3.27–3.23 (1H, m, NC*H*H), 3.11–3.06 (1H, m, NCH*H*), 3.08 (3H, s, N*Me*), 2.35–2.30 (1H, m, C(2)H_A), 1.91 (1H, dd, J=16.4, 2.8 Hz, C(2)H_B), 1.71–1.64 (1H, m, C(4)*H*), 1.44 (3H, d, J=7.1 Hz, C(α)*Me*), 1.01 and 0.84 (2×3H, d, J=6.7 Hz, Me_2CH); δ_C ($CDCl_3$, 126 MHz), 173.8 (*C*O), 143.4 (Ph_{ipso}), 139.0 (NCH_2CHCH_2), 128.0, 127.8, 126.4 (*Ph*), 115.0 (NCH_2CHCH_2), 60.6 (O*Me*), 58.1, 57.8 (*C*(α)H and *C*(3)H), 49.6 (NCH_2), 32.7 (N*Me*), 32.2 (*C*(4)H), 31.6 (*C*(2)H_2), 20.5, 20.3, 19.6 (C(α)*Me* and C(4)Me_2); *m*/*z* (CI^+, NH_3), 319 (MH^+, 100%); HRMS, $C_{19}H_{31}N_2O_2$ requires 319.2386, found, 319.2395.

4.2.7. (3*S*,α*S*)-*N*-Methoxy-*N*-methyl 3-(*N*-allyl-*N*-α-methylbenzylamino)-hexanamide 19. Following the literature procedure,[34] (*S*)-*N*-allyl-*N*-α-methylbenzylamine (746 mg, 4.64 mmol) in THF (20 mL), *n*-BuLi (2.50 M; 1.7 mL, 4.35 mmol) and **17** (455 mg, 2.9 mmol) in THF (5 mL) gave, after purification by column chromatography on silica gel, (5% EtOAc/40–60 petrol), **19** as a clear pale yellow oil (595 mg, 65%); $[\alpha]_D^{23}$=−7.5 (*c* 2.09, $CHCl_3$); ν_{max}/cm^{-1} (film) 1654 s(C=O); δ_H ($CDCl_3$, 500 MHz), 7.36–7.20 (5H, m, *Ph*), 5.97–5.89 (1H, m, NCH_2CHCH_2), 5.16 (1H, dd, J=17.2, 1.4 Hz, NCH_2CHCHH), 5.11 (1H, app d, J=10.1 Hz, NCH_2CHCHH), 4.03–4.02 (1H, m, C(α)*H*), 3.46 (3H, s, O*Me*), 3.53–3.46 (1H, m, C(3)*H*) 3.35 (1H, dd, J=15.2, 4.3 Hz, NC*H*H), 3.21–3.16 (1H, m, NCH*H*), 3.09 (3H, s, N*Me*), 2.30–2.13 (2H, m, C(2)H_2), 1.46 (3H, d, J=6.7 Hz, C(α)*Me*), 1.51–1.45, 1.33–1.26 (4H, m, C(4)H_2 and C(5)H_2), 0.88 (3H, t, J=7.1 Hz, C(6)H_3); δ_C ($CDCl_3$, 126 MHz), 173.3 (*C*O), 143.7 (Ph_{ipso}), 138.4 (NCH_2CHCH_2), 128.1, 127.9, 126.9 (*Ph*), 116.0 (NCH_2CHCH_2), 60.9, 58.6 (*C*(α)H and O*Me*), 54.1 (*C*(3)H), 49.1 (NCH_2), 35.5 (*C*(2)H_2CO), 33.8 (*C*(4)H_2), 32.0 (N*Me*), 29.7 (*C*(5)H_2), 20.0 (*C*(α)Me), 14.1 (*C*(6)H_3); *m*/*z* (CI^+, NH_3), 320 (MH^+, 100%); HRMS, $C_{19}H_{31}N_2O_2$ requires 319.2386, found, 319.2383.

4.2.8. (4*R*,α*S*)-4-*N*-Allyl-*N*-α-methylbenzylamino-5-methyl-hex-1-ene 20. DIBAL-H (1.5 M in toluene; 0.28 mL, 0.42 mmol) was added to a solution of **18** (66 mg, 0.208 mmol) in THF (3 mL) at −78°C and stirred for 3 h before the addition of acetone (1 mL). The solution was added via cannula into a saturated solution of sodium potassium tartrate (5 mL) and then extracted into Et_2O (50 mL), dried, and concentrated in vacuo. The crude product was added to a solution of phosphonium bromide/sodamide (135 mg, 0.415 mmol) in DCM (3 mL) at 0°C and warmed to rt over 18 h before the addition of pH7 buffer (1 mL), concentrated in vacuo, partitioned between DCM (2×100 mL) and water (30 mL), dried and concentrated in vacuo. Purification on silica gel, (10% Et_2O/40–60 petrol) gave **20** as a yellow oil (34 mg, 64% (2 steps); $[\alpha]_D$=−16.4 (*c* 1.53, $CHCl_3$); ν_{max}/cm^{-1} (film) 1638 s(C=C); δ_H ($CDCl_3$, 500 MHz), 7.34–7.22 (5H, m, *Ph*), 5.96–5.88 (1H, m, NCH_2CHCH_2), 5.67 (1H, ddt, J=18.3, 8.9, 7.1 Hz, C(2)*H*), 5.22 (1H, ddd, J=17.3, 3.5, 1.8 Hz, NCH_2CHCHH), 5.06 (1H, ddd, J=10.2, 3.5, 1.8 Hz, NCH_2CHCHH), 4.88–4.84 (2H, m, C(1)H_2), 3.97 (1H, q, J=6.9 Hz, C(α)*H*), 3.32–3.27 (1H, m, NC*H*H), 3.19–3.15 (1H, dd, J=15.9, 6.9 Hz, NCH*H*), 2.50 (1H, app dt, J=7.1, 4.7 Hz, C(4)*H*), 1.99–1.89 (2H, m, C(3)H_2), 1.78–1.71 (1H, m, C(5)*H*), 1.38 (3H, d, J=6.9 Hz, C(α)*Me*), 0.95 (3H, d, J=6.8 Hz, C(5)*Me*), 0.89–0.88 (3H, d, J=6.7 Hz, C(5)*Me*); δ_C ($CDCl_3$, 126 MHz), 144.9 (Ph_{ipso}), 140.0 (NCH_2CHCH_2), 138.8 (*C*(2)H), 128.0, 127.9, 126.6 (*Ph*), 114.8 (NCH_2CHCH_2), 114.6 (*C*(1)H_2), 62.5 (*C*(α)H), 59.4 (*C*(4)H), 50.2 (NCH_2CHCH_2), 33.6 (*C*(2)H_2), 31.8 (*C*(5)H), 21.5 (C(α)*Me*), 20.9, 20.4 (C(5)Me_2); *m*/*z* (CI^+, NH_3), 258 (MH^+, 100%), 216 (M−C_3H_5, 73%); HRMS, $C_{18}H_{28}N$ requires 258.2222, found, 258.2227.

4.2.9. (4*S*,α*S*)-4-*N*-Allyl-*N*-α-methylbenzylamino-hept-1-ene 21. DIBAL-H (1.5 M in toluene; 1.53 mL, 2.30 mmol) was added to a solution of **19** (365 mg, 1.15 mmol) in THF (20 mL) at −78°C and stirred for 3 h before the addition of acetone (2 mL). The solution was added via cannula into a saturated solution of sodium potassium tartrate (20 mL) and then extracted into Et_2O (2×100 mL), dried, and concentrated in vacuo. The crude product was added to a solution of phosphonium bromide/sodamide (744 mg, 2.30 mmol) in DCM (10 mL) at −40°C and warmed to rt over 12 h before the addition of pH 7 buffer (1 mL), concentrated in vacuo, partitioned between DCM (2×100 mL) and water (30 mL), dried and concentrated in vacuo. Purification by column chromatography on silica gel, (5% Et_2O/40–60 petrol) gave **21** as a clear pale yellow oil (184 mg, 62%); $[\alpha]_D^{23}$=−9.3 (*c* 1.49, $CHCl_3$); ν_{max}/cm^{-1} (film) 1639 s(C=C); δ_H ($CDCl_3$, 400 MHz), 7.40–7.25 (5H, m, *Ph*), 5.98–5.90 (1H, m, NCH_2CHCH_2), 5.69–5.61 (1H, m, C(2)*H*), 5.25 (1H, ddd, J=17.2, 3.5, 1.8 Hz, NCH_2CHCHH), 5.10 (1H, ddd, J=10.2, 3.5, 1.8 Hz, NCH_2CHCHH), 4.93–4.89 (2H, m, C(1)H_2), 4.02 (1H, q, J=6.9 Hz, C(α)*H*), 3.36–3.31 (1H, m, NC*H*H), 3.20–3.15 (1H, m, NCH*H*), 2.74–2.68 (1H, m, C(4)*H*), 2.07–2.01 (1H, m, C(3)H_A), 1.88–1.82 (1H, m, C(3)H_B), 1.58–1.49, 1.44–1.24 (4H, m, C(5)H_2 and C(6)H_2), 1.41 (3H, d, J=6.9 Hz, C(α)*Me*), 0.91–0.88 (3H, t, J=7.2 Hz, C(7)H_3); δ_C ($CDCl_3$, 126 MHz), 145.3 (Ph_{ipso}), 140.0 (NCH_2CHCH_2), 137.8 (*C*(2)H), 128.0, 127.7, 126.5 (*Ph*), 115.2 (NCH_2CHCH_2), 114.7 (*C*(1)H_2), 58.4 (*C*(α)H), 57.2 (*C*(4)H), 48.7 (NCH_2), 35.7 (*C*(3)H_2), 34.6 (*C*(5)H_2), 20.7 (C(α)*Me*), 20.2 (*C*(6)H_2), 14.3 (*C*(7)H_3); *m*/*z* (CI^+, NH_3), 258 (MH^+, 30%); HRMS, $C_{18}H_{28}N$ requires 258.2222, found 258.2223.

4.2.10. *syn*-(2*R*,3*S*,4*E*)- and *anti*-(2*S*,3*S*,4*E*)-*tert*-Butyl 2-allyl-3-(*N*-allyl-*N*-α-methylbenzylamino)-hex-4-enoate 22. LDA (2.0 M, 3.94 mL, 7.87 mmol) was added to a solution of **12** (1.73 g, 5.25 mmol) in THF and stirred for 30 min before the addition of allyl bromide (2.27 mL, 26.3 mmol) and allowed to warm to rt over 12 h. After concentration in vacuo, the residue was partitioned between DCM (100 mL) and water (25 mL), dried, and concentrated in vacuo. Purification by column chromatography on silica gel, (10% Et_2O/40–60 petrol) afforded **22** (1.92 g, 99%) as a pale yellow oil and as a mixture of diastereoisomers (d.e. 75%); (data for major diastereoisomer as minor diastereoisomer obscured); ν_{max}/cm^{-1} (film) 1728 s(C=O); δ_H ($CDCl_3$, 500 MHz), 7.39–7.19 (5H, m, *Ph*), 5.88–5.71 (2H, m, NCH_2CHCH_2 and C(2′)*H*), 5.54 (1H, dq, J=15.3, 6.4 Hz, C(5)*H*), 5.38 (1H, ddd, J=15.3, 9.9, 1.4 Hz, C(4)*H*), 5.11–4.96 (4H, m, NCH_2CHCH_2 and C(3′)H_2), 4.04 (1H, q, J=6.7 Hz, C(α)*H*), 3.56 (1H, app t, J=10.3 Hz,

C(3)*H*), 3.25 (1H, dd, *J*=14.8, 5.1 Hz, NC*H*H), 3.12 (1H, dd, *J*=14.8, 7.8 Hz, NCH*H*), 2.69–2.61 (1H, m, C(2)*H*), 2.23–2.18 (1H, m, C(1′)H_A), 2.13–2.06 (1H, m, C(1′)H_B), 1.77 (3H, dd, *J*=6.4, 1.4 Hz, C(6)H_3), 1.74 (3H, d, *J*=6.7 Hz, C(α)*Me*), 1.47 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 126 MHz), 173.6 (*C*O), 145.5 (*Ph*$_{ipso}$), 138.7, 135.6, 129.4, 128.3, 127.8, 127.6, 126.2 (NCH$_2$*C*HCH$_2$, *C*(2′)H, C(4)H, *C*(5)H and *Ph*), 116.1, 115.1 (NCH$_2$CH*C*H$_2$ and *C*(3′)H$_2$), 79.9 (*C*(CH$_3$)$_3$), 63.1 (*C*(α)H), 57.2 (*C*(3)H), 50.0 (N*C*H$_2$), 49.7 (*C*(2)H), 35.3 (*C*(1′)H$_2$), 28.1 (C(*C*H$_3$)$_3$), 18.8 (*C*(6)H$_3$), 17.9 (C(α)*Me*); *m*/*z* (APCI$^+$), 370 (MH$^+$, 100%); HRMS, $C_{24}H_{36}NO_2$ requires 370.2746, found 370.2738.

4.2.11. *syn*-(2*R*,1′*S*,4*E*,α*S*)- and *anti*-(2*S*,1′*S*,4*E*,α*S*)-*tert*-butyl 2-(1′-{*N*-allyl-*N*-α-methylbenzylamino}-but-2-enyl)-hept-6-enoate 23. LDA (2.0 M, 3.8 mL, 7.60 mmol) was added to a solution of **12** (1.66 g, 5.06 mmol) in THF (50 mL) and stirred for 30 min before the addition of 5-bromopentene (1.20 mL, 10.1 mmol) and allowed to warm to rt over 12 h. After concentration in vacuo, the residue was partitioned between DCM (100 mL) and water (25 mL), dried, and concentrated in vacuo. Purification by column chromatography on silica gel, (1–3% Et_2O/40–60 petrol), **23** as clear pale yellow oil (1.35 g, 92%) and as a mixture of diastereoisomers; data for major diastereoisomer *anti*-(2*S*,1′*S*,4*E*,α*S*)-**23**; ν_{max}/cm^{-1} (film) 1727 s(C═O); δ_H ($CDCl_3$, 400 MHz), 7.37–7.16 (5H, m, *Ph*), 5.82–5.72 (2H, m, C(6)*H* and NCH$_2$*C*HCH2), 5.48, 5.31 (2H, m, C*H*═C*H*), 5.04–4.91 (4H, m, NCH$_2$CHCH_2, C(7)H_2), 4.00 (1H, q, *J*=6.7 Hz, C(α)*H*), 3.50 (1H, app t, *J*=10.3 Hz, C(1′)*H*), 3.22 (1H, m, NC*H*H), 3.09 (1H, dd, *J*=14.8, 7.8 Hz, NCH*H*), 2.53–2.51 (1H, m, C(2)*H*), 2.08–1.96 (2H, m, C(5)H_2), 1.76–1.74 (3H, dd, *J*=6.3, 1.3 Hz, C(4′)H_3), 1.60–1.21 (4H, m, C(3)H_2, C(4)H_2), 1.49 (9H, s, C(CH_3)$_3$), 1.35 (3H, d, *J*=6.7 Hz, C(α)*Me*); δ_C ($CDCl_3$, 100 MHz), 174.5 (*C*O), 145.6 (*Ph*$_{ipso}$), 138.9, 138.6 (*C*(6)H, NCH$_2$*C*HCH$_2$), 129.1, 128.5, 128.4, 128.3, 127.8 (*C*(2′)H, *C*(3′)H and *Ph*), 115.0, 114.3 (*C*(7)H$_2$, NCH$_2$CH*C*H$_2$), 79.7 (*C*(CH$_3$)$_3$), 63.3 (*C*(α)H), 57.2 (C(1′)H), 50.1 (N*C*H$_2$), 49.7 (*C*(2)H), 33.5 (*C*(5)H$_2$), 30.3, 26.5 (*C*(4)H$_2$, *C*(3)H$_2$), 28.2 (C(*C*H$_3$)$_3$), 19.0 (C(4′)H$_3$), 18.0 (C(α)*Me*); *m*/*z* (APCI$^+$), 398 (MH$^+$, 100%), 342 (MH$^+$−C_4H_8, 25%); HRMS, $C_{26}H_{40}NO_2$ requires 398.3059, found 398.3061; selected data for minor diastereoisomer *syn*-(2*R*,1′*S*,4*E*)-**23**; ν_{max}/cm^{-1} (film) 1728 s(C═O); δ_H ($CDCl_3$, 400 MHz), 2.42–2.33 (1H, m, C(2′)*H*), 1.71 (3H, d, *J*=4.5 Hz, C(4′)H_3), 1.40 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 100 MHz), 174.4 (*C*O), 145.4 (*Ph*$_{ipso}$), 138.8, 138.5 (*C*(6)H, NCH$_2$*C*HCH$_2$), 116.0, 114.2 (*C*(7)H$_2$, NCH$_2$CH*C*H$_2$), 80.1 (*C*(CH$_3$)$_3$), 61.7 (*C*(α)H), 56.3 (C(1′)H), 50.3 (N*C*H$_2$), 28.1 (C(*C*H$_3$)$_3$).

4.2.12. (2*S*,3*S*,4*E*,α*S*)-*tert*-Butyl 2-allyl-3-(*N*-α-methylbenzylamino)-hex-4-enoate 24. $RhCl(PPh_3)_3$ (0.22 g, 0.23 mmol) was added to a refluxing solution of **22** (1.72 g, 4.64 mmol) in a MeCN–H_2O (85:15, 20 mL) and refluxed for 2 h whilst solvent was continuously replaced and azeotropic removal of propanal was effected. After concentration in vacuo, the residue was purified by column chromatography on silica gel, (3% Et_2O/40–60 petrol), to afford **24** as clear pale yellow oil (1.18 g, 77%) and as a single diastereoisomer; $[\alpha]_D^{23}$=−66.2 (*c* 1.20, $CHCl_3$); ν_{max}/cm^{-1} (film) 1728 s(C═O); δ_H ($CDCl_3$, 500 MHz), 7.34–7.20 (5H, m, *Ph*), 5.84–5.75 (1H, m, C(2′)*H*), 5.53 (1H, dq, *J*=15.2, 6.5 Hz, C(5)*H*), 5.11–5.01 (3H, m, C(4)*H* and C(3′)H_2), 3.81 (1H, q, *J*=6.4 Hz, C(α)*H*), 3.28–3.25 (1H, m, C(3)*H*), 2.33–2.26 (3H, m, C(1′)H_2 and C(2)*H*), 1.71 (3H, dd, *J*=6.4, 1.5 Hz, C(6)H_3), 1.50 (9H, s, C(CH_3)$_3$), 1.28 (3H, d, *J*=6.4 Hz, C(α)Me); δ_C ($CDCl_3$, 126 MHz), 173.4 (*C*O), 146.7 (*Ph*$_{ipso}$), 135.8, 131.6, 128.1, 126.6 (*C*(4)H, *C*(5)H, *C*(2′)H and *Ph*), 116.1 (*C*(3′)H$_2$), 79.9 (*C*(CH$_3$)$_3$), 60.0 (*C*(α)H), 54.3 (*C*(3)H), 51.9 (*C*(2)H), 34.0 (*C*(1′)H$_2$), 28.1 (C(*C*H$_3$)$_3$), 22.4 (*C*(6)H$_3$), 17.6 (C(α)*Me*); *m*/*z* (APCI$^+$), 330 (MH$^+$, 73%), 274 (MH$^+$−C_4H_8, 100%); $C_{21}H_{32}NO_2$ requires 330.2433, found 330.2430.

4.2.13. *syn*-(2*R*,1′*S*,4*E*,α*S*)-*tert*-Butyl 2-(1′-{*N*-α-methylbenzylamino}-but-2-enyl)-hept-6-enoate 25 and *anti*-(2*S*,1′*S*,4*E*,α*S*)-*tert*-butyl 2-(1′-{*N*-α-methylbenzylamino}-but-2-enyl)-hept-6-enoate 26. $RhCl(PPh_3)_3$ (0.14 g, 0.15 mmol) was added to a refluxing solution of **23** (1.2 g, 3.0 mmol) in MeCN–H_2O (85:15, 20 mL) and refluxed for 2 h whilst solvent was continuously replaced and azeotropic removal of propanal was effected. After concentration in vacuo, the residue was purified by column chromatography on silica gel, (3% Et_2O/40–60 petrol), to afford the major diastereomer *anti*-**25** (603 mg, 56%) and the minor diastereoisomer *syn*-**26** (0.240 g, 22%) as colourless oils; data for major diastereoisomer *anti*-**25**; $[\alpha]_D^{26}$=−87.3 (*c* 1.02, $CHCl_3$); ν_{max}/cm^{-1} (film) 1728 s(C═O); δ_H ($CDCl_3$, 500 MHz), 7.33–7.20 (5H, m, *Ph*), 5.81 (1H, ddt, *J*=17.0, 10.3, 6.9 Hz, C(6)*H*), 5.50 (1H, dq, *J*=15.2, 6.4 Hz, C(3′)*H*), 5.06–4.96 (3H, m, C(2′)*H* and C(7)H_2), 3.80 (1H, q, *J*=6.4 Hz, C(α)*H*), 3.22 (1H, app t, *J*=9.0 Hz, C(1′)*H*), 2.20–2.16 (1H, m, C(2)*H*), 2.10–2.00 (2H, m, C(5)H_2), 1.70 (3H, dd, *J*=6.4, 1.6 Hz, C(4′)H_3), 1.56–1.36 (4H, m, C(3)H_2, C(4)H_2), 1.51 (9H, s, C(CH_3)$_3$), 1.26 (3H, d, *J*=6.4 Hz, C(α)*Me*); δ_C ($CDCl_3$, 126 MHz), 174.2 (*C*O), 146.8 (*Ph*$_{ipso}$), 138.5, 131.8, 128.1, 127.9, 126.6 (*C*(2′)H, *C*(3′)H, *C*(6)H and *Ph*), 114.4 (*C*(7)H$_2$), 79.8 (*C*(CH$_3$)$_3$), 60.4 (*C*(α)H), 54.3 (*C*(1′)H), 52.3 (*C*(2)H), 33.5 (*C*(5)H$_2$), 29.0, 26.6 (*C*(4)H$_2$, *C*(3)H$_2$), 28.1 (C(*C*H$_3$)$_3$), 22.5 (*C*(4′)H$_3$), 17.6 (*C*(α)Me); *m*/*z* (APCI$^+$), 358 (MH$^+$, 100%), 302 (MH$^+$−C_4H_8 80%); HRMS, $C_{23}H_{36}NO_2$ requires 358.2746, found 358.2752; data for minor diastereoisomer *anti*-**26**; $[\alpha]_D^{23}$=−41.5 (*c* 0.40, $CHCl_3$); ν_{max}/cm^{-1} (film) 1728 s(C═O); δ_H ($CDCl_3$, 500 MHz), 7.36–7.21 (5H, m, *Ph*), 5.79 (1H, ddt, *J*=15.6, 10.3, 6.7 Hz, C(6)*H*), 5.48 (1H, dq, *J*=15.2, 6.4 Hz, C(3′)*H*), 5.28 (1H, ddd, *J*=15.6, 8.5, 1.6 Hz, C(7)H_A), 5.02–4.93 (2H, m, C(2′)*H* and C(7)H_B), 3.88 (1H, q, *J*=6.4 Hz, C(α)*H*), 3.11 (1H, dd, *J*=6.5, 2.0 Hz, C(1′)*H*), 2.41–2.37 (1H, m, C(2)*H*), 2.06–2.02 (2H, m, C(5)H_2), 1.66 (3H, dd, 6.4, 1.5 Hz, C(4′)H_3), 1.70–1.25 (4H, m, C(3)H_2, C(4)H_2), 1.45 (9H, s, C(CH_3)$_3$), 1.29 (3H, d, *J*=6.4 Hz, C(α)*Me*); δ_C ($CDCl_3$, 126 MHz), 173.7 (*C*O), 146.4 (*Ph*$_{ipso}$), 138.7, 131.0, 128.3, 127.6, 126.7, 126.6 (*C*(2′)H, *C*(3′)H, *C*(6)H and *Ph*), 114.4 (*C*(7)H$_2$), 80.2 (*C*(CH$_3$)$_3$), 60.5 (*C*(α)H), 54.3 (*C*(1′)H), 50.5 (*C*(2)H), 33.6 (*C*(5)H$_2$), 28.7, 26.9 (*C*(4)H$_2$, *C*(3)H$_2$), 28.2 (C(*C*H$_3$)$_3$), 23.3 (*C*(4′)H$_3$), 17.7 (*C*(α)Me); *m*/*z* (CI$^+$, NH$_3$), 358 (MH$^+$, 100%), 302 (MH$^+$−C_4H_8 22%); HRMS, $C_{23}H_{36}NO_2$ requires 358.2746, found 358.2761.

4.2.14. (2*S*,3*S*,4*E*,α*S*)-*tert*-Butyl 2-allyl-3-(*N*-α-methylbenzylamino)-*N*-benzyloxycarbonyl-hex-4-enoate 27. Dibenzyl dicarbonate (1.10 g, 3.80 mmol) was added to **24** (0.47 g, 1.27 mmol) and stirred under high vacuum for 18 h

before purification by column chromatography on silica gel, (3–6% Et_2O/40–60 petrol) to afford **27** as a colourless oil (0.50 g, 85%); $[\alpha]_D^{23}=-9.4$ (*c* 1.17, $CHCl_3$); ν_{max}/cm^{-1} (film) 1722 (CO), 1698 (NCO); δ_H (d^8 toluene, 500 MHz, at 90°C), 7.35–6.96 (10H, m, *Ph*), 5.83–5.69 (2H, m, C(2′)*H* and C(3′)H_A), 5.34 (1H, dq, *J*=19.3, 6.5 Hz, C(5)*H*), 5.05 (1H, d, *J*=12.3 Hz, N(C=O)OCH_A), 4.92 (1H, d, *J*=12.3 Hz, N(C=O)OCH_B), 4.98–4.89 (2H, m, C(3′)H_B and C(4)*H*), 4.62 (1H, q, *J*=7.0 Hz, C(α)*H*), 4.03 (1H, app. t, *J*=9.5 Hz, C(3)*H*), 3.32 (1H, dt, *J*=9.9, 4.1 Hz, C(2)*H*), 2.29–2.11 (2H, m, C(1′)H_2), 1.69 (3H, d, *J*=7.1 Hz, C(α)Me), 1.46 (3H, dd, *J*=6.5, 1.7 Hz, C(6)H_3), 1.35 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 126 MHz), 173.3 (*C*O), 155.1 (N*C*O), 141.9, 136.3 (*Ph*$_{ipso}$), 134.7 (*C*(2′)H), 130.7, 130.3, 128.0, 127.8, 127.7, 127.5, 127.2, 126.5 (*C*(4)H, *C*(5)H, *Ph*), 116.4 (*C*(3′)H_2), 80.3 (*C*(CH_3)$_3$), 66.4 (OCH_2Ph), 60.1 (*C*(α)H), 48.2 (*C*(3)H), 35.4 (*C*(1′)H_2), (*C*(2)H), 28.0 (C(CH_3)$_3$), 18.8 (*C*(6)H_3), 17.5 (C(α)*Me*); *m/z* (CI$^+$, NH_3), 464 (MH^+, 10%); HRMS, $C_{29}H_{38}NO_4$ requires 464.2801, found 464.2783.

4.2.15. (2*S*,1′*S*,4*E*,α*S*)-*tert*-Butyl 2-(1′-{*N*-benzyloxycarbonyl-*N*-α-methylbenzylamino}-but-2-enyl)-hept-6-enoate 28. Dibenzyl dicarbonate (0.94 g, 3.28 mmol) was added to *anti*-**25** (0.54 g, 1.50 mmol) and stirred under high vacuum for 18 h before purification by column chromatography on silica gel, (2–10% Et_2O/40–60 petrol) to afford **28** as a colourless oil (177 mg, 24%); $[\alpha]_D^{23}=-11.1$ (*c* 1.18, $CHCl_3$); ν_{max}/cm^{-1} (film) 1723 s(CO_2), 1698 s(NCO_2); δ_H (d^8 toluene, 500 MHz, at 90°C), 7.37–6.96 (10H, m, *Ph*), 5.82 (1H, ddd, *J*=15.4, 9.1, 1.7 Hz, C(2′)*H*), 5.69 (1H, ddt, *J*=17.0, 10.3, 6.6 Hz, C(6)*H*), 5.34 (1H, dq, *J*=15.4, 6.4 Hz, C(3′)*H*), 5.04 (1H, AB, *J*=12.3 Hz, OCH_A), 4.93 (1H, AB, *J*=12.3 Hz, OCH_B), 4.95–4.87 (2H, m, C(7)H_2), 4.61 (1H, q, *J*=7.0 Hz, C(α)*H*), 4.02 (1H, app t, *J*=9.0 Hz, C(1′)*H*), 3.30–3.24 (1H, m, C(2)*H*), 2.04–1.88 (2H, m, C(5)H_2), 1.71 (3H, d, *J*=7.0 Hz, C(α)Me), 1.48 (3H, dd, 6.4, 1.7 Hz, C(4′)H_3), 1.51–1.48 (4H, m, C(3)H_2, C(4)H_2), 1.37 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 126 MHz), 174.4 (*C*O), 155.3 (N*C*O), 142.1, 136.5 (*Ph*$_{ipso}$), 138.4, 130.2, 128.4, 128.2, 128.0, 127.8, 127.7, 127.5, 126.7 (*C*(2′)H, *C*(3′)H, *C*(6)H and *Ph*), 114.4 (*C*(7)H_2), 80.4 (*C*(CH_3)$_3$), 66.6 (O*C*H_2), 60.3 (*C*(α)H), 48.5 (*C*(1′)H), (*C*HCO$_2$),[35] 33.3 (*C*(5)H_2), 30.7, 26.2 (*C*(4)H_2, *C*(3)H_2), 28.2 (C(*C*H_3)$_3$), 18.9 (*C*(α)Me), 17.7 (*C*(4′)H_2); *m/z* (CI$^+$, NH_3), 492 (MH^+, 40%); HRMS, $C_{31}H_{42}NO_4$ requires 492.3114, found 492.3120.

4.2.16. (3*R*,4*S*,α*S*,1′*E*)-1-*N*-α-Methylbenzylamino-3-(pent-4-enyl)-4-(prop-1-enyl)-azetadin-2-one 29. TFA (2 cm^3) was added to **26** (52 mg, 0.146 mmol) and stirred at rt for 3 h before concentration in vacuo and the residue partitioned between ethyl acetate (2×15 cm^3) and a saturated aqueous solution of sodium bicarbonate (10 cm^3). The organic phases were combined, dried and concentrated in vacuo to afforded the crude carboxylic acid which was dissolved in MeCN (3 cm^3) and added to a mixture of PPh_3 (46 mg, 0.175 mmol) and dipyridyl disulphide (38 mg, 0.175 mmol) and heated for 12 h. Removal of the volatiles in vacuo and purification of the residue by column chromatography on silica gel gave **29** as a colourless oil (38 mg, 92%); $[\alpha]_D^{24}=+43.4$ (*c* 0.38, $CHCl_3$); ν_{max}/cm^{-1} (film) 1745 s(C=O); δ_H ($CDCl_3$, 400 MHz), 7.37–7.25 (5H, m, *Ph*), 5.82–5.72 (1H, m, C*H*=CH_2), 5.63 (1H, dq, *J*=15.2, 6.5 Hz, MeC*H*=CH), 5.44 (1H, ddd, *J*=15.2, 9.5, 1.5 Hz, MeCH=C*H*), 5.02–4.90 (3H, m, CH=CH_2 and C(α)*H*), 3.87 (1H, dd, *J*=9.4, 5.4 Hz, C(4)*H*), 3.08–3.03 (1H, m, C(3)*H*), 1.71 (3H, dd, *J*=6.5, 1.5 Hz, *Me*CH=CH), 1.69–1.62 (2H, m, C(3)HCH_2CH_2CH_2), 1.55 (3H, d, 7.2 Hz, C(α)*Me*), 1.52–1.36 (4H, m, C(3)HCH_2CH_2); δ_C ($CDCl_3$, 100 MHz), 170.0 (*C*O), 140.5 (*Ph*$_{ipso}$), 138.4 (C*H*=CH_2), 131.0, 128.5, 128.2, 127.4, 127.2 (Me*C*H=*C*H and *Ph*), 114.7 (CH=*C*H_2), 56.8 (*C*(α)H), 53.2 (*C*(4)H), 51.4 (*C*(3)H), 33.5 (C(3)HCH_2CH_2*C*H_2), 26.7, 24.9 (C(3)H*C*H_2*C*H_2CH_2), 19.4 (*Me*CH=CH), 17.8 (C(α)*Me*); *m/z* (APCI$^+$), 284 (MH^+, 100%); HRMS, $C_{19}H_{26}NO$ requires 284.2014, found 284.2002.

4.2.17. (*E*)-*tert*-Butyl 4-methylpenta-2,4-dienoate 30. Methacrolein (6 mL, 62.1 mmol) was added dropwise to a solution of *tert*-butyl triphenylphosphoranylideneacetate (25.7 g, 68.3 mmol) in ^{t}BuOH (50 mL) and stirred at rt for 16 h before the addition of water (20 mL) and Et_2O (2×50 mL), dried, filtered and concentrated in vacuo to give the crude product. Purification by column chromatography on silica gel, (2% Et_2O/pentane) gave **31** (3.54 g, 42%) as an oil which was stored at −25°C under N_2 to prevent polymerisation; ν_{max} (film) 1712 (C=O), 1632 (C=C), 1607 (C=C), 1151 (C–O); δ_H ($CDCl_3$, 400 MHz) 7.27 (1H, d, *J*=15.8 Hz, C(3)*H*), 5.81 (1H, d, *J*=15.8 Hz, C(2)*H*), 5.33 (1H, br s, C(5)H_B), 5.31 (1H, br s, C(5)H_A), 1.88 (3, s, C(4)*Me*), 1.51 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 50 MHz) 146.2, 140.8 (*C*(2), (*C*(1)), 135.3 (*C*(4)), 123.8 (*C*(5)), 120.8 (*C*(3)), 80.3 (*C*(CH_3)$_3$), 28.0 (C(CH_3)$_3$), 18.0 (C(4)*Me*); *m/z* (CI$^+$, NH_3) 186 (MNH_4^+, 86%), 169 (MH^+, 100); HRMS $C_{10}H_{17}O_2$ requires 169.1230, found 169.1231.

4.2.18. (2*S*,3*R*,α*S*)-*tert*-Butyl 2-(prop-2-enyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methylpent-4-enoate 31. Following the literature procedure,[18] (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (3.0 g, 14.3 mmol) in THF (20 mL), *n*-BuLi (1.6 M, 18.7 mL, 13.9 mmol) and **30** (2.0 g, 11.9 mmol) in THF (5 mL) gave, after addition of allyl bromide (1.5 mL, 17.8 mmol) and purification by column chromatography on silica gel, (2% Et_2O/pentane) and recrystallisation (Et_2O/pentane), **31** as a white solid (1.8 g, 36%). Found, C, 79.9; H, 8.8; N, 3.2%; $C_{28}H_{37}NO_2$ requires: C, 80.15; H, 8.9; N, 3.35%; mp 62–63°C; $[\alpha]_D^{23}=-37.0$ (*c* 0.2, $CHCl_3$); ν_{max} (KBr) 1720 (C=O), 1642 (C=C), 1604 (C=C), 1164 (C–O); δ_H ($CDCl_3$, 400 MHz) 7.18–7.37 (10H, m, *Ph*), 5.60 (1H, m, C(2)HCH_2C*H*=C*H*H), 5.02 (1H, br s, C(5)H_B), 4.97 (1H, d, *J*=17.0 Hz, C(2)HCH_2CH=CH*H*), 4.92 (1H, d, *J*=10.1 Hz, C(2)HCH_2CH=C*H*H), 4.77 (1H, br s, C(5)H_A), 4.14 (1H, q, *J*=6.9 Hz, C(α)*H*), 3.81, 4.09 (2H, AB, *J*=14.5 Hz, NCH_2Ph), 3.51 (1H, d, *J*=10.6 Hz, C(3)*H*), 2.76 (1H, dt, *J*=10.6, 4.2 Hz, C(2)*H*), 1.98–2.05 (2H, m, C(2)HCH_2), 1.77 (3H, s, C(4)*Me*), 1.45 (9H, s, OC(CH_3)$_3$), 1.38 (3H, d, *J*=6.9 Hz, C(α)*Me*); δ_C ($CDCl_3$, 50 MHz) 174.1 (*C*O), 143.5, 144.6 (*Ph*$_{ipso}$), 141.6 (*C*(4)), 135.8 (C(2)HCH_2*C*H=CH_2), 126.7, 127.9, 128.0, 128.5 and 128.9 (*Ph*$_{o\text{-},m\text{-},p\text{-}}$), 116.5, 116.6 (*C*(5)$H_2$, C(2)HC$H_2$CH=C*H*$_2$), 80.6 (O*C*(CH$_3$)$_3$), 65.3 (C(α)*H*), 57.8 (*C*(3)), 50.9 (NCH_2Ph), 47.9 (*C*(2)), 35.3 (C(2)*C*H_2), 28.1 (C(*C*H_3)$_3$), 21.4 (C(α)*Me*), 16.0 (C(4)*Me*); *m/z* (APCI$^+$) 420 (MH^+, 100%).

X-Ray crystal structure data for **31**. Data were collected using an Enraf-Nonius CAD4 diffractometer with graphite monochromated Cu Kα radiation using standard procedures at rt. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[36] Crystal data for **31** [$C_{28}H_{38}NO_2$], colourless block, M=420.59, orthorhombic, space group $P2_12_12_1$, a=9.275(1) Å, b=10.472(1) Å, c=26.912(6) Å, U=2613.88(1) Å^3, Z=4, μ=0.509, crystal dimensions 0.5×0.5×1.0 mm. A total of 3040 unique reflections were measured for $0<\theta<74.33$ and 2472 reflections were used in the refinement. The final parameters were wR_2=0.0711 and R_1=0.0572 [$I>3\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 197300.

4.2.19. (2*R*,α*S*)-*tert*-Butyl 1-(*N*-α-methylbenzylamino)-2,5-dihydro-1*H*-2-pyrrolyl-acetate 32. Following representative procedure 1, **13** (2.0 g, 6.29 mmol) in DCM (200 mL) and ruthenium alkylidene **1** (0.20 g, 0.25 mmol) gave, after purification by column chromatography (3–5% Et_2O/40–60 petrol), **32** (1.4 g, 77%) as a clear yellow oil; $[\alpha]_D^{24}=-132.0$ (*c* 0.99, $CHCl_3$); ν_{max}/cm^{-1} (film) 1728 s(C=O); δ_H ($CDCl_3$, 500 MHz), 7.36–7.22 (5H, m, *Ph*), 5.78–5.70 (2H, m, C(3)*H*=C(4)*H*), 4.21–4.16 (1H, m, C(2)*H*), 3.88 (1H, q, *J*=6.7 Hz, C(α)*H*), 3.64–3.60 (1H, m, C(5)H_A), 3.43–3.38 (1H, m, C(5)H_B), 2.62 (1H, dd, *J*=14.5, 4.0 Hz, C(1′)H_A), 2.37 (1H, dd, *J*=14.5, 8.9 Hz, C(1′)H_B), 1.49 (9H, s, C(CH_3)$_3$), 1.46 (3H, d, *J*=6.7 Hz, C(α)*Me*), δ_C ($CDCl_3$, 126 MHz), 171.3 (*C*O), 144.7 (*Ph*$_{ipso}$), 130.6, 128.2, 127.3, 126.8, 126.6 (*C*(3)H=*C*(4)H and *Ph*), 80.0 (*C*(CH_3)$_3$), 64.7 (*C*(1)H), 62.0 (Me*C*HN), 58.3 (*C*(3)H_2), 43.0 (*C*(1′)H_2), 28.0 (C(*C*H_3)$_3$), 22.8 (C(α)*Me*); *m*/*z* (APCI$^+$), 288 (MH$^+$, 80%), 219 (MH$^+-C_4H_8$, 100%); HRMS, $C_{18}H_{26}NO_2$ requires 288.1963, found, 288.1967.

4.2.20. (2*S*,α*S*)-Methyl 2-(*N*-α-methylbenzylamino)-1,2,3,6-tetrahydro-2-pyridinyl-acetate 33. Following representative procedure 1, **15** (1.28 g, 4.3 mmol) in DCM (200 mL) and **1** (0.14 g, 0.17 mmol) gave, after purification by column chromatography, first on neutral alumina then on silica gel, (5% Et_2O/40–60 petrol) **33** as clear yellow oil (0.54 g, 49%); $[\alpha]_D^{25}=+11.0$ (*c* 1.01, $CHCl_3$); ν_{max}/cm^{-1} (film) 1736 s(C=O); δ_H ($CDCl_3$, 500 MHz), 7.38–7.22 (5H, m, *Ph*), 5.71 (2H, m, C(4)*H*=C(5)*H*), 3.63–3.54 (1H, m, C(α)*H*), 3.60 (3H, s, O*Me*), 3.42–3.38 (1H, m, C(6)H_A), 3.35–3.31 (1H, m, C(2)*H*), 3.00–2.95 (1H, m, C(6)H_B), 2.56 (1H, dd, *J*=14.2, 3.9 Hz, C(1′)H_A), 2.39–2.36 (1H, m, C(3)H_A), 2.33 (1H, dd, *J*=14.2, 9.5 Hz, C(1′)H_B), 1.85–1.80 (1H, m, C(3)H_B), 1.35 (3H, d, *J*=6.6 Hz, C(α)*Me*); δ_C ($CDCl_3$, 126 MHz), 173.6 (*C*O_2), 145.6 (*Ph*$_{ipso}$), 128.4, 127.1, 126.9, 125.2, 123.2 (*C*(4)H=*C*(5)H and *Ph*), 60.9 (O*C*H_3), 51.4 (*C*(α)H), 49.2 (*C*(2)H), 44.6 (*C*(6)H_2), 30.6 (*C*(1′)H_2), 29.1 (*C*(3)H_2), 22.2 (C(α)*Me*); *m*/*z* (APCI$^+$), 260 (MH$^+$, 100); HRMS, $C_{16}H_{22}NO_2$ requires 260.1651, found 260.1655.

4.2.21. (2*R*,α*S*)-1-*N*-α-Methylbenzylamino-2-isopropyl-1,2,3,6-tetrahydropyridine 34. Following representative procedure 1, **20** (34 mg, 0.13 mmol) in DCM (9 mL) and **1** (4 mg, 0.005 mmol) gave, after purification by column chromatography, first on neutral alumina then on silica gel, (2–10% Et_2O/40–60 petrol) **34** as clear yellow oil (22 mg, 78%); $[\alpha]_D^{23}=-2.0$ (*c* 0.66, $CHCl_3$); ν_{max}/cm^{-1} (film) 1653 w(C=C); δ_H ($CDCl_3$, 500 MHz), 7.46–7.25 (5H, m, *Ph*), 5.80–5.75, 5.66–5.62 (2H, m, C(4)*H* and C(5)*H*), 4.09 (1H, q, *J*=6.6 Hz, C(α)*H*), 3.22–3.11 (2H, m, NC(6)H_2), 2.45–2.42 (1H, m, C(2)*H*), 2.24–2.19 (1H, m, C(3)H_A), 2.09–2.02 (1H, m, Me_2C*H*), 1.99–1.95 (1H, m, C(3)H_B), 1.36 (3H, d, *J*=6.6 Hz, C(α)*Me*), 1.04 (3H, d, *J*=6.8 Hz, *Me*CH), 0.91 (3H, d, *J*=6.7 Hz, *Me*CH); δ_C ($CDCl_3$, 126 MHz), 146.1 (*Ph*$_{ipso}$), 128.1, 127.5, 126.4, 125.4, 124.6 (*Ph*, *C*(4)H and *C*(5)H), 58.4 (*C*(α)H), 57.4 (*C*(2)H), 42.2 (*C*(6)H_2), 27.7 (Me_2*C*H), 22.6 (*C*(3)H_2), 20.6 (C(α)*Me*), 18.9, 18.0 (*Me*$_2$CH); *m*/*z* (APCI$^+$), 230 (MH$^+$, 5%), 105 (PhCHCH_3, 100%); HRMS, $C_{16}H_{24}N$ requires 230.1909, found 230.1911.

4.2.22. (2*S*,α*S*)-1-*N*-α-Methylbenzylamino-2-propyl-1,2,3,6-tetrahydropyridine 35. Following representative procedure 1, **21** (80 mg, 0.31 mmol) in DCM (20 mL) and **1** (10 mg, 0.012 mmol) gave, after purification by column chromatography, first on neutral alumina then on silica gel, (5–10% Et_2O/40–60 petrol) **34** as clear yellow oil (64 mg, 91%); $[\alpha]_D^{23}=-11.3$ (*c* 1.9, $CHCl_3$); ν_{max}/cm^{-1} (film) 1601 w(C=C); δ_H ($CDCl_3$, 400 MHz), 7.44–7.26 (5H, m, *Ph*), 5.74–5.71 (1H, ddd, *J*=9.9, 5.0, 2.4 Hz, C(4)*H*), 5.62–5.59 (1H, app. dd, *J*=9.9, 2.4 Hz, C(5)*H*), 3.77–3.73 (1H, q, *J*=6.6 Hz, C(α)*H*), 3.18–3.15 (1H, m, C(2)*H*), 3.02–2.98 (1H, app. d, *J*=17.5 Hz, C(6)H_A), 2.92–2.88 (1H, app. d, *J*=17.5 Hz, C(6)H_B), 2.47–2.42 (1H, m, C(3)H_A), 2.01–1.97 (1H, m, C(3)H_B), 1.60–1.56, 1.47–1.32 (4H, m, MeCH_2 CH_2), 1.39–1.38 (3H, d, *J*=6.6 Hz, C(α)*Me*), 1.01–0.98 (3H, t, *J*=7.1 Hz, *Me*CH_2); δ_C ($CDCl_3$, 126 MHz), 146.3 (Ph$_{ipso}$), 128.2, 127.4, 126.6, 125.4, 123.5 (*Ph*, *C*(4)H, *C*(5)H), 60.3 (*C*(α)H), 51.2 (*C*(2)H), 45.2 (*C*(6)H_2), 28.5 (*C*(3)H_2), 27.8 (MeCH_2*C*H_2) 20.8 (C(α)*Me*), 20.1 (Me*C*H_2 CH_2), 14.4 (*Me*CH_2); *m*/*z* (APCI$^+$), 230 (MH$^+$, 75%); HRMS, $C_{16}H_{24}N$ requires *m*/*z* 230.1910, found 230.1907.

4.2.23. (1*S*,2*S*,α*S*)-*tert*-Butyl 2-*N*-α-methylbenzylamino-*N*-benzyloxycarbonyl-cyclopent-3-ene-1-carboxylate 36. Following representative procedure 1, **27** (130 mg, 0.28 mmol) in DCM (22 mL) and **1** (12 mg, 0.014 mmol) gave, after heating 1 h and purification by column chromatography on silica gel, (5–10% Et_2O/40–60 petrol), **36** as clear yellow oil (102 mg, 86%); $[\alpha]_D^{23}=+68.1$ (*c* 2.19, $CHCl_3$); ν_{max}/cm^{-1} (film) 1728 s(CO), 1694 s(NCO); δ_H (d^8 toluene, 500 MHz, at 90°C), 7.31–6.92 (10H, m, *Ph*), 5.53–5.50 (1H, m, C(3)*H*), 5.37–5.33 (2H, m, C(2)*H* and C(4)*H*), 4.98 (2H, s, OCH_2Ph), 4.85 (1H, q, *J*=7.0 Hz, C(α)*H*), 3.04–3.00 (1H, m, C(1)*H*), 2.57–2.40 (2H, m, C(5)H_2), 1.52–1.51 (3H, d, *J*=7.0 Hz, C(α)Me), 1.30 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 126 MHz), 174.1 (*C*O), 155.8 (N*C*O), 142.0, 136.3 (*Ph*$_{ipso}$), 132.4, 129.6, 128.2, 127.9, 127.8, 126.7, 126.6 (*C*(3)H, *C*(4)H, *Ph*), 80.3 (*C*(CH_3)$_3$), 67.0 (O*C*H_2Ph), 67.0 (*C*(2)*H*), 53.2 (*C*(α)H), 47.5 (*C*(1)H), 36.5 (*C*(5)H_2), 27.8 (C(*C*H_3)$_3$), 18.4 (C(α)*Me*); *m*/*z* (CI$^+$, NH_3), 422 (M$^+$, 100%), 366 (M$-C_4H_8$, 64%); HRMS, $C_{26}H_{32}NO_4$ requires 422.2331, found 422.2321.

4.2.24. (1*S*,2*S*)-*tert*-Butyl 2-(1′-{*N*-benzyloxycarbonyl-*N*-α-methylbenzylamino}-cyclohept-3-ene-1-carboxylate 37. Following representative procedure 1, **28** (85 mg,

0.17 mmol) in THF (11 mL) and **1** (6 mg, 0.006 mmol) gave, after heating for 2 h and purification by column chromatography on silica gel, (2–10% Et_2O/40–60 petrol), **37** as a colourless oil (61 mg, 78%); $[\alpha]_D^{23}$=+30.2 (*c* 1.08, $CHCl_3$); ν_{max}/cm^{-1} (film) 1724 s(CO_2), 1702 s(NCO_2); δ_H (d^8 toluene, 500 MHz, at 90°C), 7.40–6.96 (10H, m, *Ph*), 5.62–5.59 (1H, m, C(3)*H*), 5.48–5.43 (1H, m, C(4)*H*), 5.09 (1H, AB, *J*=12.4 Hz, OCH_A), 5.03 (1H, AB, *J*=12.4 Hz, OCH_B), 4.78 (1H, q, *J*=7.0 Hz, C(α)*H*), 4.63–4.62 (1H, m, C(2)*H*), 3.16 (1H, dt, *J*=9.3, 3.2 Hz, C(1)*H*), 1.98–1.87 (2H, m, C(7)H_2), 1.98–1.87, 1.68–1.61, 1.49–1.44, 1.25–1.18 (4H, m, C(5)H_2, C(6)H_2), 1.69 (3H, d, *J*=7.0 Hz, C(α)*Me*), 1.32 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 126 MHz), 174.3 (*C*O), 156.0 (N*C*O), 142.5, 137.0 (*Ph*$_{ipso}$), 133.8, 128.5, 128.3, 128.1, 127.7, 127.0 (*C*(3)H, *C*(4)H and *Ph*), 80.1 (*C*(CH_3)$_3$), 66.9 (O*C*H_2), 61.4 (*C*(α)H), 59.9 (C(2)*H*), 49.0 (*C*(1)H), 31.0 (*C*(7)H_2), 28.2 (C(*C*H_3)$_3$), 27.0, 24.0 (*C*(5)H_2, *C*(6)H_2), 19.7 (C(α)*Me*); *m/z* (CI^+, NH_3), 450 (MH^+, 10%); HRMS, $C_{28}H_{36}NO_4$ requires 450.2644, found, 450.2636.

4.2.25. (1*R*,7*S*,α*S*)-8-(*N*-α-Methylbenzylamino)-8-azabicyclo[5.2.0]non-5-ene-9-one 38. Following representative procedure 1, *syn*-**29** (38 mg, 0.13 mmol) in DCM (10 mL) and **1** (4 mg, 0.005 mmol) gave, after heating for 2 h and purification by column chromatography on silica gel, (40% Et_2O/40–60 petrol), **38** as a colourless oil (30 mg, 93%); $[\alpha]_D^{24}$=+10.5 (*c* 0.53, $CHCl_3$); ν_{max}/cm^{-1} (film) 1736 s(C=O); δ_H ($CDCl_3$, 400 MHz), 7.39–7.27 (5H, m, *Ph*), 5.61–5.54 (2H, m, C(5)*H*, C(6)*H*), 4.98 (1H, q, *J*=7.2 Hz, C(α)*H*), 4.17–4.15 (1H, m, C(7)*H*), 3.11 (1H, dt, *J*=10.0, 5.3 Hz, C(1)*H*), 2.13–2.08 (2H, m, *C*(4)H_2), 1.95–1.83, 1.63–1.46 (4H, m, *C*(2)H_2, *C*(3)H_2), 1.66 (3H, d, *J*=7.2 Hz, C(α)*Me*); δ_C ($CDCl_3$, 126 MHz), 170.1 (*C*O), 140.3 (*Ph*$_{ipso}$), 128.8, 128.7, 127.6, 127.0, 126.1 (*C*(5)H, *C*(6)H, and *Ph*), 54.0 (*C*(α)H), 51.8, 51.4 (*C*(7)H, *C*(1)H), 26.6 (*C*(4)H_2), 23.1, 20.3 (*C*(3)H_2, *C*(2)H_2), 19.6 (C(α)Me); *m/z* ($APCI^+$), 242 (MH^+, 100%); HRMS, $C_{16}H_{20}NO$ requires 242.1545, found 242.1543.

4.2.26. (1*S*,2*R*,α*S*)-*tert*-Butyl 3-methyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopent-3-ene-1-carboxylate 39. Following representative procedure 1, **31** (600 mg, 1.43 mmol) in DCM (200 mL) and **1** (5 mg, 0.5 mmol) gave, after purification by column chromatography (2% Et_2O/pentane) **39** (195 mg, 35% at 50% conversion). Found: C, 79.55; H, 8.5; N, 3.4%; $C_{26}H_{33}NO_2$ requires: C, 79.75; H, 8.5; N, 3.6%; $[\alpha]_D^{23}$=+61.4 (*c* 0.1, $CHCl_3$); ν_{max} (film) 1724 (C=O), 1144 (C–O); δ_H ($CDCl_3$, 400 MHz) 7.19–7.45 (10H, m, *Ph*), 5.37 (1H, br s, C(4)*H*), 4.20 (1H, br s, C(2)*H*), 3.90 (1H, q, *J*=6.8 Hz, C(α)*H*), 3.51, 3.76 (2H, AB, *J*=15.1 Hz, NCH_2Ph), 2.61 (1H, m, C(1)*H*), 2.57 (1H, m, C(5)H_B), 2.31 (1H, m, C(5)H_A), 1.82 (3H, s, C(3)*Me*), 1.40 (9H, s, OC(CH_3)$_3$), 1.29 (3H, d, *J*=6.8 Hz, C(α)*Me*); δ_C ($CDCl_3$, 50 MHz) 176.1 (*C*O), 142.5, 144.6 (*Ph*$_{ipso}$), 140.8 (*C*(3), 126.4, 126.8, 127.8, 128.0, 128.3 and 128.4 (*Ph*$_{o\text{-},m\text{-},p\text{-}}$), 125.6 (*C*(4)), 79.9 (O*C*(CH_3)$_3$), 71.0 (*C*(2)), 59.7 (C(α)*H*), 49.9 (N*C*H_2), 42.9 (*C*(1)), 36.4 (*C*(5)), 27.9 (C(*C*H_3)$_3$), 22.1 (C(α)*Me*), 14.5 (C(3)*Me*); *m/z* ($APCI^+$) 392 (MH^+, 90%).

4.2.27. (*S*)-Methyl piperidin-2-yl-acetate 40. 10% Pd on C (10 mg) was added to a degassed solution of **33** (71 mg, 0.27 mmol) in MeOH (5 mL) and stirred under 5 atm of hydrogen for 18 h at 50°C. The crude reaction mixture was filtered through a plug of Celite®, and concentrated in vacuo before purification by chromatography on silica gel, (20% MeOH/Et_2O) to give **40** as clear pale yellow oil (40 mg, 93%); $[\alpha]_D^{26}$=+3.9 (*c* 0.64, $CHCl_3$); ν_{max}/cm^{-1} (film) 1736 s(C=O); δ_H ($CDCl_3$, 500 MHz), 3.68 (3H, s, O*Me*), 3.13–3.10 (1H, m, C(6)H_A), 2.99–2.92 (2H, m, N*H* and C(2)*H*), 2.68 (1H, app. dt, *J*=11.9, 2.5 Hz, C(6)H_B), 2.48–2.45 (2H, m, C(1′)H_2), 1.82–1.79, 1.68–1.61, 1.53–1.23 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2); δ_C ($CDCl_3$, 126 MHz), 172.5 (*C*O_2), 53.2 (O*Me*), 51.6 (*C*(2)H), 46.4 (*C*(6)H_2), 40.7 (*C*(1′)H_2), 29.7 (*C*(5)H_2), 25.3, 24.2 (*C*(4)H_2, *C*(5)H_2); *m/z* ($APCI^+$), 158 (MH^+, 100%); $C_8H_{16}NO_2$ requires 158.1181, found 158.1179.

4.2.28. (*S*)-Homopipecolic acid 41. Amino ester **40** (30 mg, 0.19 mmol) was refluxed in hydrochloric acid (2 M, 10 mL) for 4 h before concentration in vacuo. The residue was subjected to ion exchange chromatography on Dowex 50WX8-200 resin giving **41** as a pale yellow waxy oil (25 mg, 92%); $[\alpha]_D^{26}$=+24.0 (*c* 0.87, H_2O), lit.[23] $[\alpha]_D$=+22.1 (*c* 0.6, H_2O)}; ν_{max}/cm^{-1} (film) 1711 s(C=O); δ_H (D_2O, 500 MHz), 3.37–3.27 (2H, m, C(6)H_A and C(2)*H*), 2.95–2.89 (1H, m, C(6)H_B), 2.44 (2H, app d, *J*=6.6 Hz, C(1′)H_2), 1.85–1.77 and 1.58–1.39 (2×3H, m, C(3)H_2, C(4)H_2 and C(5)H_2); δ_C ($CDCl_3$, 126 MHz), 177.1 (*C*O_2), 54.4 (*C*(2)H), 44.7 (*C*(6)H_2), 39.6 (*C*(1′)H_2), 28.1 (*C*(5)H_2), 21.9, 21.5 (*C*(4)H_2 and *C*(5)H_2); *m/z* ($APCI^+$), 144 (MH^+, 100%); HRMS, $C_7H_{14}NO_2$ requires 144.1025, found 144.1023.

4.2.29. (2*S*,α*S*)-*tert*-Butyl 1-(*N*-α-methylbenzylamino)-pyrrolidin-2-yl-acetate 42. $RhCl(PPh_3)_3$ (100 mg) was added to a degassed solution of **32** (1.0 g, 3.5 mmol) in benzene (5 mL) and stirred under 2 atm of H_2 at rt. The resultant mixture was filtered through Celite®, concentrated in vacuo and purified by chromatography on silica gel, (10% Et_2O/pentane) to give **42** (865 mg, 86%) as a colourless oil; $[\alpha]_D^{23}$=−56.1 (*c* 1.6, $CHCl_3$), ν_{max}/cm^{-1} ($CHCl_3$) 1727 s(C=O); δ_H ($CDCl_3$, 400 MHz), 7.34–7.24 (5H, m, *Ph*), 3.78 (1H, q, *J*=6.8 Hz, C(α)*H*), 3.08–3.03 (1H, m, C(2)*H*), 2.82–2.77 (1H, m, C(5)H_A), 2.60 (1H, dd, *J*=14.2, 2.6 Hz, C(1′)H_A), 2.40–2.34 (1H, m, C(5)H_B), 2.20 (1H, dd, *J*=14.2, 10.0 Hz, C(1′)H_B), 1.88–1.58 (4H, m, C(3)H_2 and C(4)H_2), 1.46 (3H, d, *J*=6.8 Hz, C(α)*Me*), 1.44 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 100 MHz), 171.9 (*C*O_2), 142.7 (*Ph*$_{ipso}$), 128.0, 127.9, 126.8 (*Ph*), 80.0 (*C*(CH_3)$_3$), 60.3 (*C*(α)H), 57.0 (*C*(2)H), 49.7 (*C*(5)H_2), 41.5 (*C*(1′)H_2), 30.6, 22.6 (*C*(4)H_2 and *C*(3)H_2), 28.1 (C(*C*H_3)$_3$), 22.1 (C(α)*Me*); *m/z* ($APCI^+$), 290 (MH^+, 10%), 234 ($MH^+-C_4H_8$ 100%); HRMS, $C_{18}H_{28}NO_2$ requires 290.2120, found 290.2126.

4.2.30. (*S*)-*tert*-Butyl pyrrolidin-2-yl-acetate 43. 20% $Pd(OH)_2$ on C (250 mg) was added to a degassed solution of **42** (500 mg) in MeOH–H_2O–acetic acid (40:4:1) (45 mL) and stirred under 1 atm of H_2 for 12 h at rt. The crude reaction mixture was filtered through a plug of Celite®, concentrated in vacuo, dissolved in DCM (5 mL) and washed with sat aq. bicarbonate, dried, concentrated and purified by chromatography on silica gel, (20% MeOH/$CHCl_3$) to give **43** as a pale yellow oil (295 mg, 92%); $[\alpha]_D^{23}$=+1.0 (*c* 1.55, $CHCl_3$), {lit.[37] $[\alpha]_D^{27}$=+1.5 (*c* 0.99, $CHCl_3$)}; ν_{max}/cm^{-1} ($CHCl_3$) 1728 s(C=O); δ_H ($CDCl_3$, 500 MHz), 3.87–3.81 (1H, m, NC*H*CH_2), 3.38–3.35 (2H,

m, NCH_2), 3.09–3.04 (1H, dd, J=16.9, 5.9 Hz, $CHHCO$), 2.77–2.72 (1H, dd, J=16.9, 8.2 Hz, $CHHCO_2$), 2.30–2.24 (1H, m, NCH_2CH_2CHH), 2.09–1.95 (2H, m, NCH_2CH_2), 1.74–1.67 (1H, m, NCH_2CH_2CHH), 1.42 (9H, s, $C(CH_3)_3$); δ_C ($CDCl_3$, 126 MHz), 169.1 (CO_2), 81.7 ($C(CH_3)_3$), 55.9 ($NCHCH_2$), 44.7 (NCH_2), 37.3 (CH_2CO), 30.2, 23.4 ($NCHCH_2$ and NCH_2CH_2), 28.0 ($C(CH_3)_3$); m/z ($APCI^+$), 186 (MH^+, 10%), 130 ($MH^+-C_4H_8$ 100%).

4.2.31. (*S*)-Homoproline 44. HCl_{aq} (1 M, 20 mL) was added to **43** (200 mg) and stirred at rt for 12 h before concentration in vacuo. Purification by ion exchange chromatography (Dowex 50WX8-200) gave **44** (134 mg, 96%) as a white solid; $[\alpha]_D^{23}$=+3.4 (c 1.0, H_2O); lit.[26] $[\alpha]_D^{25}$=+4.0 (c 1.0, H_2O); δ_H (D_2O, 400 MHz), 3.70–3.63 (1H, m, C(2)H), 3.23–3.13 (2H, m, C(5)H_2), 2.53–2.41 (2H, m, C(1′)H_2), 2.12–2.03 (1H, m, C(3)H_A), 1.99–1.80 (2H, m, C(4)H_2), 1.60–1.50 (1H, m, C(3)H_A).

4.2.32. (*S*)-(+)-Coniine hydrochloride 45. A solution of **35** (38 mg, 0.148 mmol) in degassed MeOH (2 mL) was hydrogenated at 5 atm over 10% palladium on carbon (15 mg) for 12 h at rt before filtration through a pad of Celite® eluting with Et_2O. The resultant solution was cooled to 0°C and treated with HCl gas and stirred at rt for 10 minutes before concentration in vacuo. Purification by column chromatography on silica (5% MeOH/DCM) gave **45** (23 mg, 95%) as a white solid; mp 195°C (lit.[38] mp 205°C); {$[\alpha]_D^{21}$=+8.3 (c 0.7, EtOH); lit. $[\alpha]_D^{25}$=+9.4 (c 0.32, EtOH);[30] $[\alpha]_D^{25}$=+8.1 (c 0.6, EtOH)[31]}; δ_H ($CDCl_3$, 400 MHz), 9.6–9.0 (2H, bm, NH·HCl), 3.60–3.35 (1H, bm, C(2)H), 3.00–2.90 (1H, m, C(6)H_A), 2.85–2.75 (1H, m, C(6)H_B), 2.21–1.36 (10H, m, C(3)H_2, C(4)H_2, C(5)H_2, C(1′)H_2 and C(2′)H_2), 1.05–0.80 (3H, bm, Me).

4.2.33. (1*S*,2*S*)-2-Aminocyclopentanecarboxylic acid hydrochloride 46. 10% palladium on carbon (20 mg) was added to a degassed solution of **36** (93 mg, 0.220 mmol) in glacial acetic acid (3 mL) and hydrogenated under 5 atm of hydrogen for 18 h at 50°C. The crude reaction mixture was filtered through Celite®, concentrated in vacuo then treated with an ethereal solution of hydrochloric acid (20 mL). The resulting solution was stirred for 20 min at rt before concentration in vacuo, giving **46** (30 mg, 73%) as a white solid; $[\alpha]_D^{22}$=+46.4 (c 1.04, H_2O), {lit.[32] $[\alpha]_D^{28}$=−50.7 (c 0.75, H_2O) for enantiomer}; δ_H (D_2O, 300 MHz), 3.79–3.68 (1H, m, C(2)H), 2.82–2.70 (1H, m, C(1)H), 2.15–2.00, 1.81–1.50 (6H, m, (C(3)H_2, C(4)H_2, C(5)H_2).

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